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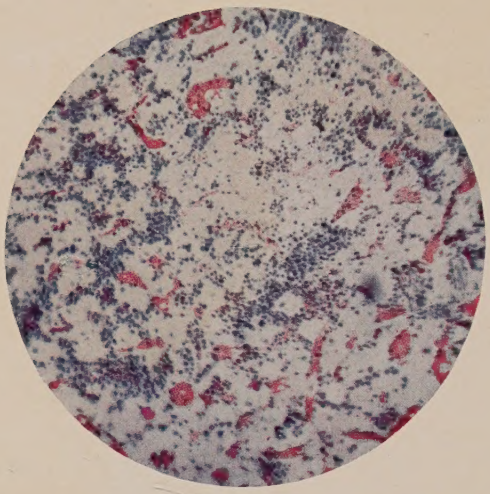
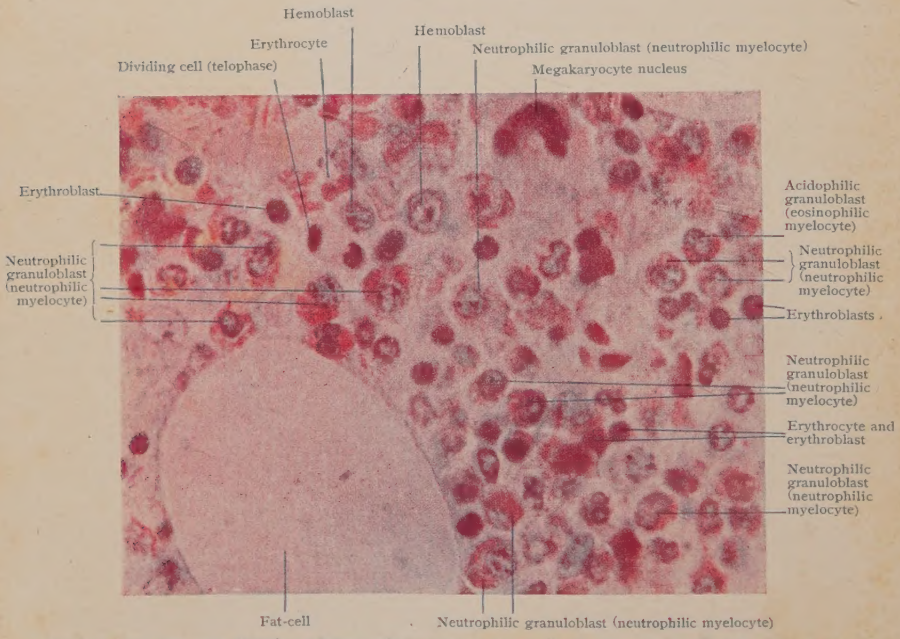
ENDOCHONDRAL BONE DEVELOPMENT

1. Formation of fetal hyaline cartilage from precartilage mesenchyma.
2. Enlargement of the cartilage cells with a rearrangement into radiating cell rows at the center of ossification.
3. Absorption of the cartilage matrix between the cells of the rows and finally also of the cells themselves. Calcification of persistent remnants ofcartilage matrix between the rows of cells.
4. Eruption of the subperiosteal osteogenic tissue, invasion to the center of cartilage plate, and the formation of primary marrow cavities at the cente of ossification.
5. Gradual extension of the above processes followed by a deposit of primary bone by the osteoblasts upon the calcified cartilage spicules. Coincident osteoblastic deposit of perichondrial bone beneath and within the perichon rium of the cartilage plate.
6. Absorption of portions of the primary bone by the osteoclaststo form the large central marrow cavity or medulla. The absorption involves both the endochondral and the perichondral bone and is accopanied by a furthar deposit ofnew bone at the periphery.In the perichondrial bone cylindrical axial channels are formed, in which the deposit of new bone produces the Haversion systems of the compact boney tissue.

PLATE I.



Bone marrow, showing arrangement of cellular areas. (From femur of Rhesus monkey; fixation, formol-Zenker fluid of Helly; stain, azur II and eosin) × 90.



Human bone marrow, showing a hemopoietic centre; from rib of man, 26 years old. × 1000.
(Prepared by the Ellermann technic; the originals of both illustrations were made by color-photography by Dr. M. N. Richter.)

THOROUGHLY REVISED AND RESET

PIERSOL'S
NORMAL HISTOLOGY

WITH SPECIAL REFERENCE TO THE STRUCTURE
OF THE HUMAN BODY

THIRTEENTH EDITION NOW FIRST EDITED
AND IN PART REWRITTEN

BY

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432 ILLUSTRATIONS, 43 OF WHICH ARE IN COLOR

PHILADELPHIA AND LONDON
J. B. LIPPINCOTT COMPANY

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Printed by J. B. Lippincott Company
The Washington Square Press, Philadelphia, U.S.A.

EDITOR'S PREFACE

In the preparation of the present edition, the aim has been to make the descriptions of the normal human tissues minute enough to serve as a basis for the study of pathological histology, which is concerned with material obtained chiefly from autopsies, and to a less extent, from surgical operations. For this reason careful attention has been given to those organs which are usually taken at autopsies, and emphasis is laid upon their conspicuous features. This method of presenting the salient features first rests upon well-tried pedagogical principles, and by its use the student early acquires confidence in his own powers of observation. When he has once laid a sure foundation by seeing the characteristic structural arrangement of an organ or tissue and by relating it with the written description, he is prepared to continue its study by both observation of special preparations and by reading the results of original investigation. For guidance in the latter, a selection of references to current literature has been added, based on reading-lists prepared for class use. As part of the routine classwork, each student during the term should read and report on one or more of these papers, or others selected by the instructor.

The parts of the book relating to protoplasm, cell-structure and cell-division have been rewritten, and the descriptions of bone-marrow, blood-development and blood-cells have been greatly amplified and illustrated with additional figures. The endocrine glands have been grouped together in conformity with present usage.

References are made to the results of the newer methods of study of living cells, such as microdissection, tissue-cultures, and supravital staining, and descriptions of these methods are given in the appendix. The frozen section method for the rapid preparation of tissue, and the parlodion embedding method are included under technic.

I am indebted to many of my friends and colleagues for assistance in various ways, especially to Dr. M. N. Richter for bone-marrow material and photomicrographs in color; to Dr. C. L. Parmenter for preparations of chromosomes; to Dr. Joseph McFarland for the loan of sections showing different functional conditions of the mammary gland; to Dr. Cecil K. Drinker for the use of figures of injected bone-marrow; to Dr. M. J. Hogue for writing the descriptions of methods of study of living cells; to Dr. J. Howard Smith for assistance in obtaining material at autopsy; to Mr. B. B. Varian for additions to microscopic technic, to Miss Doris A. Fraser for assistance with the manuscript and proof; and to Mr. E. F. Faber for the new drawings.

University of Pennsylvania, 1926. W. H. F. A.

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NORMAL HISTOLOGY

PROTOPLASM AND THE CELL

Protoplasm has been defined as "the physical basis of life." All living organisms consist essentially of protoplasm, and all their activities depend upon its properties. About two-thirds of this protoplasm, by weight, is water, with which organic and inorganic compounds stand in close chemical and physical relation. Protoplasm may be regarded as a colloidal system, of which there are multiple varieties. These may consist of solid substances dispersed in a water medium, as in the softer tissues, or conversely, water dispersed in a solid medium, as in bone. Each variety is continually changing, and the greatest change occurs when the protoplasm dies. When protoplasm ceases to live, certain of these colloidal systems are altered so that they are no longer colloidal. Some of the suspended aggregates disappear and larger ones appear as a result of the irreversible chemical changes which occur upon the death of the cell. The term protoplasm as used above refers to the entire series of body tissues.

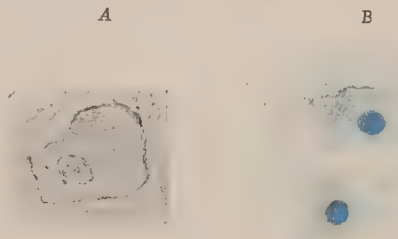


FIG. 1—Squamous epithelial cells, from the tongue: *A*, living unstained; *B*, stained with methylene blue.

By examining with the microscope a drop of blood, or a scraping from the inner surface of the lip, examples of living protoplasm may be readily studied. The protoplasm is arranged in small discrete masses called **cells**, which are the elements of structure of living organisms. Cells are of multiple shapes and sizes, but all have certain structural characteristics in common by which they may be recognized. For instance, each has within it a differentiated body, the **nucleus**, so that a cell has been defined as "a minute nucleated mass of protoplasm." The protoplasm of a cell is thus composed of the **karyoplasm** of the nucleus, and the **cytoplasm** of the cytosome, or cell-body. The boundary of the nucleus is emarginated by a nuclear membrane, and the boundary of the cytoplasm by a plasma-membrane, or plasmolemma.

Chemically, protoplasm consists of a heterogeneous mixture of water, salts, and organic compounds. The latter are present largely as **proteins**, which in water exist as a colloidal solution. There are also simpler nitrogenous substances, which are called extractives, present in all tissue extracts. Glycogen and fat are found in many cells, and are demonstrable under the microscope by the use of special methods. The inorganic substances include

salts of sodium, potassium, calcium, magnesium, and iron. These salts are chiefly the chlorides, bicarbonates, phosphates, and sulphates. Proteins and other organic substances also form salts. One of the most important functions of these salts is to aid in the control of the chemical neutrality of the cells.

The fundamental part of living protoplasm is in the form of a colloid which is optically homogeneous. Within this colloidal system there exist aggregates, some of which are only to be seen with the ultra-microscope and others which are large enough to be visible through the ordinary bright-field microscope. When protoplasm is killed and "fixed" by reagents, coagulations and other changes take place, which produce striking alteration in its appearance. Thus, in studying the appearances in preserved cells, one should correlate these with the structures to be seen in the living cells. This correlation has been made more precise by the present day development of the methods of tissue-cultures and of microdissection of cells. It is

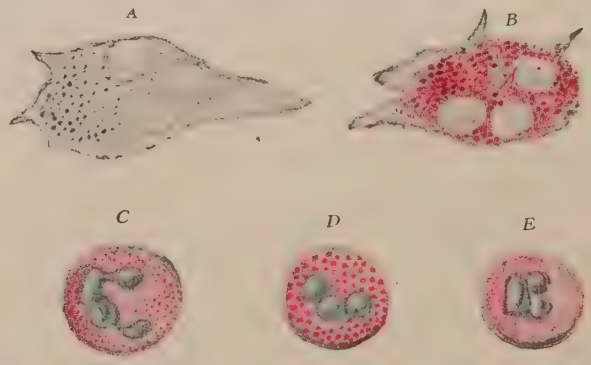


FIG. 2—Leucocytes of the blood.—*A*, living, unstained, on warm stage, at body temperature; *B*, living, supravitally stained with neutral red (p. 435); *C*, fixed as thin film, smear preparation, stained on slide (p. 456); *D*, in section of bone-marrow after special technic of Ellerman (p. 435); *E*, in section of bone-marrow after routine fixation and staining.

also a fact that different fixing fluids produce different effects on the constituents of the same protoplasm. Thus not all fixing fluids preserve certain substances and structures seen in the living, as fat, mitochondria, and the granules in the leucocytes of blood. This means that, for a complete picture, one must study cells prepared by different methods. It is only by bringing together the results of all methods, that it is possible to give a complete, though composite, picture of any type of cell, and so to understand its activities.

There are two usages of the term protoplasm, which must be noted at this point. While in its wider application, as used above, protoplasm refers to living matter in general, in its narrower sense it refers only to the cytoplasmic portions of the cells.

Morphologically, the fundamental unit of structure of all animals and plants is the cell. With the exception of the unicellular forms, in which a single cell constitutes the entire organism, the fully developed animal comprises myriads of cells arranged as the tissues composing the various parts or organs.

Notwithstanding its complexity, the body of any vertebrate, including that of man, may be resolved into four elementary tissues—**epithelial, connective, muscular,** and **nervous**—which serve, primarily, for the purpose of protection, connection and support, motion and control respectively. Every tissue consists of two parts, the cells and the intercellular substance. Upon the first of these, the cells, depend the vitality and growth of the tissue, and also the production of intercellular substance.

The higher animals are derived from the union of the parent cells, the **sperm** and the **ovum.** This latter element, liberated from the ovary of the mother, undergoes certain preparatory changes, known as maturation and then unites with the paternal germ-cell, the sperm or spermatozoön, which has gone through similar preparatory stages. The union of these two sex-cells constitutes the fertilization of the ovum. The fertilized ovum then divides into two daughter-cells, each of which gives rise to two new elements; each of these, in turn, produces two descendants, and so on. As the result of **segmentation,** as this cycle of repeated division is termed, a numerous progeny of new cells arises from the original parent-cells. The further division and differentiation of the segmenting cells lead to the formation of the three **germ-layers**—the **ectoderm,** the **mesoderm,** and the **entoderm**—from which the definite embryo subsequently is evolved.

THE STRUCTURE OF THE CELL

The two essential parts of a cell are the cell-body and the nucleus.

The Cell-body, or Cytosome.—The translucent plastic substance forming the cell-body is the cytoplasm. The physical characters of the cytoplasm exhibit considerable variations in different types of cell, and also in different physiological conditions of the same cell. The consistency varies from a stiff, jelly-like state to a fluid condition. The optical appearance is that of a homogeneous ground-substance in which are usually seen minute particles of varied shapes and sizes. Because of these, the cytoplasm by no means always presents the same structural appearance. Thus, the cytoplasm may be devoid of recognizable definite structure and appear *homogeneous;* at other times it may present aggregations of minute spherical particles and then be described as *granular,* or where the minute spheres are larger and consist of fluid substances embedded within a surrounding denser material, as *reticular;* or, again, and very frequently, the cytoplasm contains threads or fibrils, more or less conspicuous, which arrangement gives rise to the *fibrillar* condition.

The homogeneous substance is regarded as the fundamental ever-present part of the cytoplasm, and is termed **hyaloplasm.** The visible structures suspended within it are the **formed bodies** of the cytoplasm. Some of these are to be seen only in preserved states of the cell. Many of the specialized activities of different types of cells are associated with the presence of different formed bodies.

The **formed bodies** include: (1), centrosomes, (2) secretory granules and their antecedents, (3) storage material, (4) pigment granules, (5) fibrillæ,

(6) mitochondria, (7) Golgi-apparatus, or "internal reticular apparatus" of Golgi. Some of these bodies are more readily demonstrated than others.

1. The **centrosome** is of widespread occurrence in the cells of higher animals, and is of importance in cell-division, as well as in other cellular activities. During cell-division it is conspicuous in being the focus of the astral rays, as described later under mitosis. Ordinarily the centrosome is not discernible because, on account of its minute size and variable staining affinity, it is with difficulty distinguished from surrounding bodies. Often it is composed of two little dot-like structures, lying side by side. Its exact position within the cytosome seems to depend upon the locus of greatest cellular activity; thus, in a dividing cell, the centrosome lies in close relation with the actively changing nuclear elements, while within ciliated epithelium it is found closely associated with the contractile filaments connected

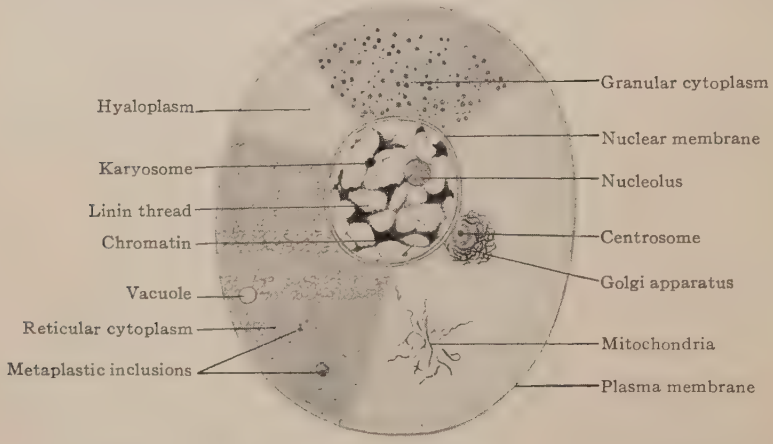


FIG. 3—Diagram of cell-structure. In the upper part of figure the granular condition of the cytoplasm is represented; in the lower and left part, the reticular condition.

with the vibratory hair-like appendages. Because of the intimate relations between this minute body and the active changes affecting the cell, the centrosome may be regarded physiologically as its dynamic centre.

2. **Secretory granules** are of widespread occurrence in secreting cells, whether aggregated to form glands or scattered singly. They are of plastic and transitory nature, and contribute an important part of the secretion. Their number, size, and appearance change with the several stages involved in the elaboration and discharge of the secretion. Distinct examples are seen in the cells of the pancreas and of the hypophysis.

3. **Storage materials** in the form of granules and globules are often called "metaplasmic inclusions," and are regarded as secondary products of protoplasmic activity. They include glycogen, fat, and the yolk granules of the embryonic cells.

4. **Pigment granules** usually appear as minute separate bodies, often closely crowded together. Examples are shown in the pigmented epithelium of the retina, and in the nerve-cells of the adult.

5 **Fibrillæ** are characteristic of fixed preparations of skeletal and cardiac muscle-cells and of nerve-cells. In the muscle-cells the myofibrils are parallel in arrangement, while in the nerve-cells they form a more interlacing net.

6. **Mitochondria** are found in nearly all varieties of cells, but they change so rapidly after death that they are only infrequently demonstrable in human autopsy material. They are small elements of various forms—granules, rods, or filaments, and in living cells, as seen in tissue-cultures, are continually undergoing change of position and often of shape. They are soluble in dilute acetic acid, and this differentiates them from most secretory granules. They are imperfectly preserved or even disappear entirely in many of the ordinary fixing agents.

7. The "**internal reticular apparatus**" of Golgi is the name given to structures seen by the use of certain special methods. As first described by Golgi in the nerve-cells of the spinal ganglia they have the appearance of a net-like structure. It usually lies at one side of the nucleus, but sometimes extends all about it. In glandular cells, it typically lies on the side toward the lumen, and this suggests a relationship with the secretory function.

FIG. 4—Spermatogenic cells, showing variations in the condition and the arrangement of the constituents of the cytoplasm and the nucleus; the centrosomes are seen within the cytoplasm close to the nucleus. *A*, from the guinea-pig, × 1675 (*Meves*): *B*, from the cat, × 680 (*von Lenhossek*).

The Nucleus.—This usually appears as a sharply defined spherical or ellipsoidal body, which, in stained preparations, is conspicuous on account of its deeper color. The nucleus in sections usually shows four distinct components: **nuclear membrane; nuclear framework,** in the form of a net or reticulum; **nuclear matrix,** or ground-substance, occupying the meshes of the network; and one or more **nucleoli,** which are distinct rounded bodies. The nucleus is relatively large in young, actively growing elements since it is important in the nutritive as well as the reproductive activities of the cell. While, in a general way, the nucleus corresponds in shape to the form of the cell, being oval or rod-like in elongated columnar or fusiform cells, and compressed or flattened in plate-like elements, its outline is sometimes very irregular, as conspicuously seen in the case of the granular leucocytes of the blood. At times the nucleus is capable of changing its form or even position independent of the surrounding cytoplasm.

The **nuclear membrane** is a definite film, which in some cases is very tough and elastic. Thus, by the microdissection method some nuclei may be stretched to ten times the length of their usual diameter and return to their original form and size (Seifriz). The nuclear membrane persists

throughout the life of a cell, until the time of beginning cell-division, when it disappears. As the nuclei of the two daughter-cells take form again, the membrane reappears.

The **nuclear framework,** when examined under high magnification after treatment with suitable stains, is seen to consist of a double structure. Most evident are minute irregular masses of a deeply stained substance, appropriately called **chromatin,** in recognition of its great affinity for certain coloring-matters. The chromatin particles are supported upon or within delicate inconspicuous and almost colorless threads of **linin.** The latter forms the basis of the nuclear framework in which the chromatin is so conspicuous by reason of its capacity for staining. The individual masses of chromatin vary greatly in form, often being irregular, and at other times thread-like or beaded. Not infrequently the chromatin presents spherical aggregations which appear as deeply stained nodules attached to the nuclear

FIG. 5—Internal reticular apparatus of Golgi in epithelial cells of epididymis (*after Nassonov, '24*).

FIG. 6—Mitochondria and internal reticular apparatus of Golgi, in epithelial cells of epididymis (*after Nassonov, '24*).

framework. These constitute the false nucleoli, or **karyosomes,** as distinguished from the true nucleolus, which is usually present within the karyoplasm. Chemically, chromatin, the most important part of the nucleus, contains **nuclein,** a compound rich in phosphorus.

The **nuclear matrix** or *sap*, the semi-fluid substance which occupies the spaces in the nuclear framework, possesses an exceedingly weak affinity for the staining reagents employed to color the chromatin. It usually appears, by comparison, therefore, clear and untinted.

The **nucleolus,** or *plasmosome*, ordinarily appears as a small spherical body, sometimes multiple, lying within, but unattached to, the nuclear framework. In stained tissues its color varies, sometimes resembling that of the chromatin, although less intense, but usually presenting a different tint, since it responds readily to dyes which, like eosin or acid fuchsin, particularly affect the linin and cytoplasm. Concerning the nature, purpose and function of the nucleolus much uncertainty exists.

Vital Phenomena.—The manifestations of the life of the cell include the changes which occur during the performance of its work. Vital phe-

nomena are probably governed by the same physico-chemical laws that govern non-living matter. Such phenomena embrace **metabolism, growth, reproduction,** and **irritability.**

Metabolism, the most distinctive characteristic of living matter, is that process whereby protoplasm selects from the heterogeneous materials of food those particular substances which are suitable for its nutrition and converts them into its own substance. Metabolism is of two kinds—constructive and destructive. Constructive metabolism, or **anabolism,** is the process by which the cell converts simple compounds into more complex compounds. Destructive metabolism, or **katabolism,** is the process by which the cell breaks up the complex substances resulting from constructive metabolism into simpler compounds. Vegetal cells possess the power of constructive metabolism in a conspicuous degree, and from the simple substances, water, carbon dioxide, and inorganic salts, prepare food-material, which can be utilized by animal cells in their nutritive and katabolic processes. Animal cells, then, are dependent, directly or indirectly, upon the vegetal cells for their nutritive materials.

Growth, the natural sequel of the nutritive changes effected by metabolism, may be unrestricted and equal in all directions, resulting in uniform expansion of the spherical cell, as illustrated in the growth of the ovum. Such unrestricted growth, however, is exceptional, since cells are usually so intimately related to one another that their shape is modified by mutual pressure, and they become polyhedral. F. T. Lewis has recently studied the exact form of cells in masses, such as fat cells and stratified epithelial cells lining the mouth cavity. He finds they are usually of fourteen sides (tetrakaidecahedral), and conform to an ideal geometrical design which encloses the greatest mass with the least surface (Lewis, '25). Examples of the results of unequal specialized growth are seen in the fibres of muscular tissue and the neurones of the nervous system.

Reproduction may be regarded as the culminating vital manifestation in the life-cycle of the cell, since by this process the parent-cell surrenders individuality and continues its life in the existence of its offspring. Cell-reproduction occurs by two methods—the indirect, or **mitotic,** and the direct, or **amitotic.** The first of these, involving the complicated cycle of nuclear changes known as **mitosis,** or *karyokinesis*, is the usual method; the second and simpler process of direct division is exceptional.

Irritability is that property of living matter by virtue of which the cell exhibits changes in its intimate constitution in response to external stimuli. The latter may be mechanical, thermal, electrical, or chemical in nature; or they may be produced in consequence of obscure and subtle changes occurring within the protoplasm of neighboring cells, as illustrated by the reaction of one neurone in response to the stimuli transmitted from other nervous elements.

CELL-DIVISION

The production of new generations of cells of all kinds is usually accomplished by a complicated series of changes collectively known as **mitosis,** or *karyokinesis*, in which the nucleus plays a prominent part. Of the various

constituents of the nucleus the chromatin displays the most active behavior, and this substance is regarded as the main vehicle by which the characteristics of the parent-cell are transmitted to the new elements. So essential is this substance for the perpetuation of the specific character of the cell, that the entire mitotic cycle has for its primary purpose the insurance of equal division of the chromatin of the mother-cell between the two new nuclei.

Mitosis, *or Indirect Cell-division.*—This includes the series of changes undergone by the karyoplasm and the cytoplasm in the process of one cell dividing into two cells. According to Donaldson there are 12,000 million

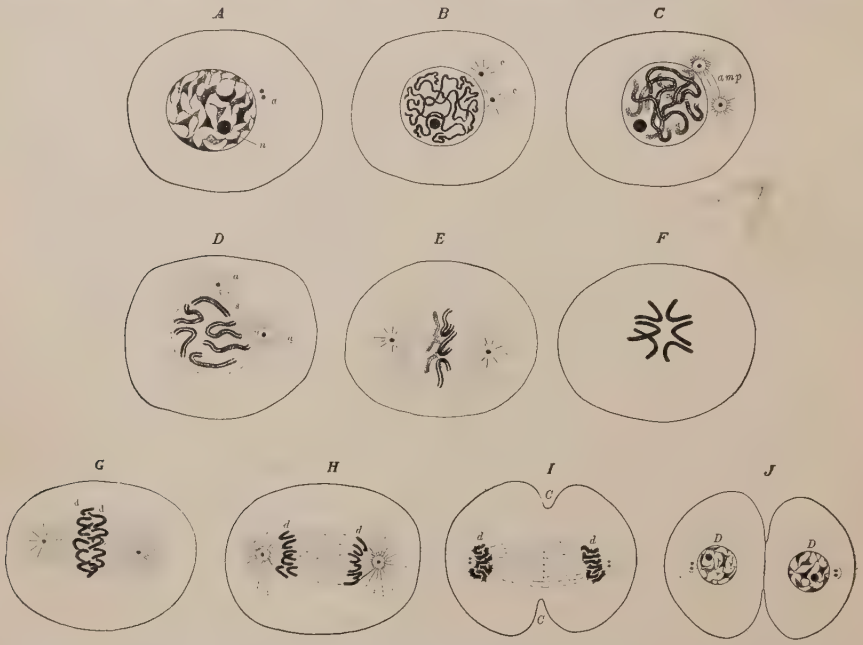


FIG. 7—Diagram of mitosis. *A*, so-called resting stage, chromatin irregularly distributed in nuclear reticulum; *a*, centrosome divided; *n*, nucleolus. *B*, chromatin forming finely convoluted threads (spireme-threads); centrosomes (*c*) separating, each surrounded by a star-shaped aster. *C*, chromatin-threads shorter and thicker, plainly split; nuclear membrane disappearing; amphiaster (*amp*) forming. *D*, chromosomes irregularly distributed among the spindle-fibres (*s*) of the amphiaster. *E*, lateral aspect of metaphase; the split chromosomes arranged in the equatorial plane of the spindle (equatorial plate). *F*, polar view of the preceding. *G*, early anaphase; the two daughter-halves (*d*) of each split chromosome separating from one another towards opposite poles of the cell. *H*, late anaphase; the two groups of daughter-chromosomes approaching the opposite poles of the spindle. *I*, *J*, telophases; the chromatin of the chromosomes becoming rearranged to form the so-called resting condition, represented in *J*; the cell-body is constricting, and in *J* the division becomes completed.

cells in the cortex of the cerebral hemispheres of the human brain. These are all formed by the process of mitosis and all before birth, so that nearly 12,000 million mitoses have occurred in the prenatal period in forming the cells of this region alone.

Mitosis is a continuous process, but for descriptive purposes it may be subdivided into four stages: (1) the **prophases,** or period of formation of the chromatin-threads and the first indication of their splitting; (2) the **metaphases,** during which the chromosomes are plainly double, each consisting of two longitudinal halves, still in close apposition; (3) the **anaphases,** in which

the two halves of each chromosome separate and move towards opposite ends of the cell; (4) the **telophases,** during which the two duplicate sets of chromosomes become grouped at the two opposite poles of the cell, and then gradually pass into the condition of the so-called resting nucleus, and the cytosome of the mother-cell becomes constricted into two parts, each containing the reconstructing nucleus (Figs. 7 and 8).

The essential nuclear features of mitosis are: (1) the rearrangement of the chromatin and linin of the so-called resting nucleus to form a number of discrete linear parts, the chromosomes (48 in man); (2) each chromosome

FIG. 8—Mitotic figures in the division of epithelial cells of skin of salamander embryo. *A*, so-called resting condition; *B*, early condition of spireme-threads; *C*, spireme-threads shorter and thicker, longitudinal splits visible in places; *D* and *E*, early metaphases, polar view, longitudinal splits indistinct; *F*, metaphase, polar view, daughter-halves of each chromosome are distinct: *G*, oblique view of metaphase; *H*, anaphase, daughter-chromosomes separating and migrating to opposite poles of the cell, not all chromosomes shown; *I*, a very late anaphase in which daughter-chromosomes have migrated to either pole of the cell, and the cell-body is dividing. (*From preparations made by G. A. Piersol*).

splits longitudinally, the split often appearing while each chromosome is still a linear series of granules or chromomeres; each chromosome eventually divides into two halves, alike in size, form, and qualities; (3) the number of chromosomes is the same in all somatic cells of an individual, and the number is the same in all the individuals of the same sex of any one species; the number, however, is not the same in all species: for example, in man it is forty-eight, opossum twenty-two, frog twenty-six, house-fly twelve; (4) in all cells with an even number of chromosomes there is a duplicate series of chromosomes, one half the number being originally of maternal origin, the other half of paternal origin. Each chromosome from the ovum

has its counterpart derived from the sperm; (5) the individual chromosomes often have characteristic differences of size and form, as shown in specially prepared material (Fig. 9).

The **Prophases** (Fig. 7) include a series of changes which involve the nuclear substances and the centrosome, and result in the production of the **mitotic figure.** The latter consists of two parts, (1) the **chromatin,** which stains deeply, and (2) the **achromatic figure,** which colors only slightly or not at all. The chromatin, which in the non-dividing nucleus shows as small masses scattered in the nuclear framework, takes on the form of fine convoluted threads. On account of the interwoven, skein-like appearance of the chromatic substance, this is known as the **spireme-formation** and the chromatin threads are called **spireme-threads.** These separate threads gradually shorten and thicken and become the **chromosomes.** During these changes, affecting the chromatin, the **nucleolus,** or plasmosome, disappears and probably takes no active part in mitosis. After definite formation of the chromosomes the nuclear membrane likewise disappears, so that the karyoplasm and cytoplasm are now continuous.

Coincident with the foregoing changes, the achromatic figure develops.

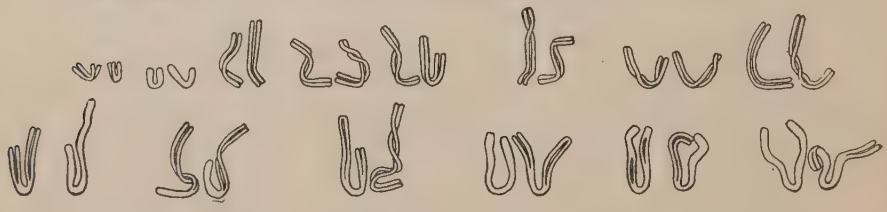


FIG. 9—The chromosomes of the somatic cells of a salamander, arranged in pairs. One of each pair is of maternal origin and the other is of paternal origin. (*From Parmenter, '19*).

The centrosome is already double, usually having divided into two bodies at the end of the previous mitosis. During the interval they have remained close together, but now they begin to move apart. Around each centrosome a delicate radial striation appears, resembling the rays of a star, and hence called an **aster** (Fig. 7, B). The two asters remain in continuity by certain of their rays, and the whole achromatic figure is the **amphiaster.** As the two centrosomes with their surrounding asters continue to migrate towards opposite poles of the cell, the intervening connective fibres are necessarily elongated and these constitute the **nuclear spindle.** It is within this nuclear spindle that the chromosomes come to lie, and become attached to certain fibres of the spindle. The centrosomes play an important rôle in establishing foci towards which the new daughter-chromosomes will move after they are formed by the division of the parent-chromosome. The preparation for this division is early manifested. Already in the early prophase the substance of the spireme-threads becomes arranged into two longitudinal parts, quantitatively and qualitatively equal. The two halves remain in close apposition while the chromosomes are taking on their definite form. The different chromosomes may be of various shapes, for example—spheres, rods, J-, U-, and V-shapes. Each of the chromosomes, moreover, when fully formed has a definite size and shape, by which it may often be distinguished.

The **Metaphases** are the stages in which the chromosomes are arranged in the equatorial plane of the nuclear spindle in readiness for the separation of each of their two halves. This is a stage of relative stability in which the mitotic figure may remain for a considerable time. The chromosomes are definitely double in character, and the spindle-fibres have a definite point of attachment to each half of the chromosome. In the so-called **polar view,** the smaller chromosomes are seen to be centrally placed, surrounded by an outer ring of larger chromosomes (Fig. 10).

During the **Anaphases,** the two halves of each chromosome separate and move in opposite directions along the nuclear spindle towards the centrosomes at the two ends of the spindle. The daughter-chromosomes always begin to separate at the point of attachment of the spindle-fibres. Thus, in rod-shaped chromosomes, the attachment is often terminal and then the process of separation begins at one end and continues towards the other end. As the two parts gradually separate the dividing chromosome first assumes a Y-shape, and then a V-shape, and finally there are two rod-shaped daughter-chromosomes. In chromosomes of a curved or bent shape, such as V-shaped chromosomes, seen in growing root-tips of plants and in epithelial cells of salamander-larvæ, the attachment is usually at the angle. In these, the separation begins at the apex of the angle and gradually progresses along both the arms towards their ends, forming irregular ring- or diamond-shapes, until there is finally complete separation. As the receding segments pass towards their respective poles, the opposed ends of the separating daughter-chromosomes are united by intervening achromatic threads, the **connecting fibres.** Sometimes the latter exhibit a linear series of thickenings at their mid-points, collectively known as the **cell-plate,** or *mid-body.* There thus results the grouping of a duplicate series of chromosomes at either pole of the cell. By this procedure the numerical constancy of the chromosomes is maintained throughout successive generations of cells. Moreover, not only the number, but also the individual characters of the chromosomes are reproduced in each of the two groups which are later to constitute the chromatin of the two daughter-cells.

FIG. 10—Spermiogenesis; metaphase. (*From Winiwarter and Oguma, '25*).

During the **Telophases,** the daughter-nuclei are reconstructed from the two groups of daughter-chromosomes, and division of the cell-body takes place. After the migration of the chromosomes to either pole is completed, the chromosomes lose their characteristic form and the chromatin becomes dispersed in small masses. In some types of cells, the chromatin formerly constituting each chromosome can be seen definitely separated from that of the others, and in the next succeeding mitosis this chromatin reconstitutes a chromosome of the same size, shape, and quality as that of the preceding division (Wenrich, '16). In such cases there would be a continuity of the individual chromosomes through successive generations of cells. Mean-

while a nuclear membrane has formed around each daughter-nucleus. In addition, during these final stages of mitosis, the cell-body gradually constricts. The furrow deepens until the division of the cell into two is completed, the plane of the division coinciding with the equator of the nuclear spindle. The new cell, now possessing all the constituents of the parent-element, usually acquires the morphological characteristics of its ancestor and passes into a condition of comparative rest, until called upon, in its turn, to undergo division and enter upon the complicated cycle of mitosis.

The Time-interval of Mitosis.—Two or three hours would be a fair estimate of the total time involved from the beginning of prophase until the so-called resting stage is reached, according to W. H. Lewis and M. R. Lewis ('17, '24). Their conclusions are based on observations of living cells in tissue-cultures. The cells appear as grayish gelatinous expansions, in which the nucleus and other structures are distinguishable by reason of their higher refractive indices. Many of the minutiæ described above are not visible in the living cell, and some may be artificial. The interval from the first visible nuclear changes until the chromosomes are arranged in the equatorial plane is thirty to sixty minutes. The period from the time the chromosomes are first arranged in the equatorial plane until they begin to move toward the poles varies from one to fifteen minutes, and sometimes lasts longer. The time occupied by the migration of the chromosomes to the poles averages two to three minutes. The interval from the time the chromosomes become grouped at each pole (end of anaphase) until there are two separate cells is three to six minutes. There is an appreciable interval between the end of anaphase and the first appearance of the indentation, averaging one to two minutes. From the first appearance of the indentation until complete division, the time averages two to four minutes. This is followed by a reconstruction period, during which the nuclear membranes appear, and the chromatin becomes arranged as in the so-called resting condition. The limit of this is difficult to determine, but lies between thirty to one hundred and twenty minutes. Thus it is seen that the preliminary and terminal phenomena occupy the greater part of the two to three hours involved.

Chromosomes of Germ-cells.—The notable exception to the constancy of the numerical quota of the chromosomes presented by the germ-cells should be mentioned. Since the chromosomes of the fertilized ovum are derived from the chromatin contributed equally by the paternal and maternal germ-cells—the sperm and the ovum—it is evident that unless the number of chromosomes from each parent be only one-half the usual number for the species, the segmentation nucleus and the succeeding cells would contain twice the normal quota of chromosomes. In order to prevent such redundancy, during the development of the spermatic cells, on the one hand, and the maturation of the ovum on the other, **reduction** of the chromosomes to one-half the usual number actually takes place. The details by which this reduction is accomplished vary in different classes of animals; but, whatever be the method, the result is to reduce the number of chromatin-masses one-half. The full quota for the species is restored to the segmentation nucleus and its descendants by the subsequent addition of the reduced contingents of the two germ-cells when fertilization occurs.

SYNOPSIS OF MITOTIC DIVISION

I. Prophases:

A. Changes within the nucleus: Chromatic figure.

Formation of chromatin-threads from the nuclear material of the so-called resting nuclei.
Fine spireme, of long, thin, interwoven chromatin-threads (spireme-threads).
Appearance of two longitudinal halves in each chromatin-thread.
Shortening and thickening of chromatin-threads (coarse spireme).
Definitive chromosomes.

B. Changes within the cytoplasm: Achromatic figure.

Division of centrosome.
Appearance of asters.
Migration of centrosomes and asters.
Formation of amphiaster.
Appearance of nuclear spindle.

II. Metaphase:

Arrangement of the chromosomes to form the equatorial plate.

III. Anaphases:

Separation of the two halves of each chromosome.
Migration of daughter-chromosomes towards opposite poles of amphiaster.
Appearance of connecting fibres between receding groups.

IV. Telophases:

Chromosomes lose definite form, and chromatin more diffusely arranged.
Appearance of nuclear membranes.
Appearance of nucleoli.
Constriction of cell-body at right angles to axis of spindle.
Daughter-nuclei assume so-called resting condition.
Complete division of cell-body.
Centrosomes, single or double, lie beside new nuclei.

Amitotic Division.—The occurrence of cell-reproduction without the complex cycle of karyokinetic changes is known as **amitotic,** or *direct division*. The essential difference between the direct and the usual method of division lies in the fact that the amitotic process results in mass-division of the nucleus without insuring the equal apportionment of the chromatin or the continuance of the normal quota of chromosomes, as is accomplished by the mitotic cycle. Neither the chromatic figure nor the achromatic spindle is produced and the influence of the centrosome is uncertain. The division of the cytosome often lags behind that of the nucleus, resulting in the production of binucleate cells and cells with multiple nuclei. In a careful study of binucleate cells produced in this manner in tissue-cultures, Macklin ('16) saw no cell in which amitotic nuclear division was followed by division of the cytosome. The process is regarded by some as allied to nuclear fragmentation. It has been suggested that interference with the normal nutritive supply may bring about amitotic division and

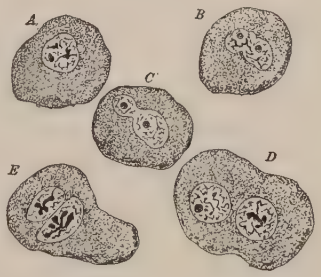


FIG. 11—Decidual cells exhibiting amitotic division of nucleus (*A-D*); in *E* irregular mitosis has occurred. × 350.

that it may be a device to increase the nuclear surface. In addition to the blastodermic cells of the embryo, nuclear amitosis has been described in the epithelium of the skin and bladder.

ORIGIN AND DIFFERENTIATION OF THE CELLS

The body, with all its complex details, is the product of the differentiation and specialization of cells which are the descendants of the fertilized ovum. The latter represents the two parents, since the chromatin of the segmentation nucleus is contributed equally by the germ-cells, the sperm, and the ovum.

The **ovum** is formed within the female sexual gland, the **ovary,** where it passes through all stages of development, from immaturity to maturation,

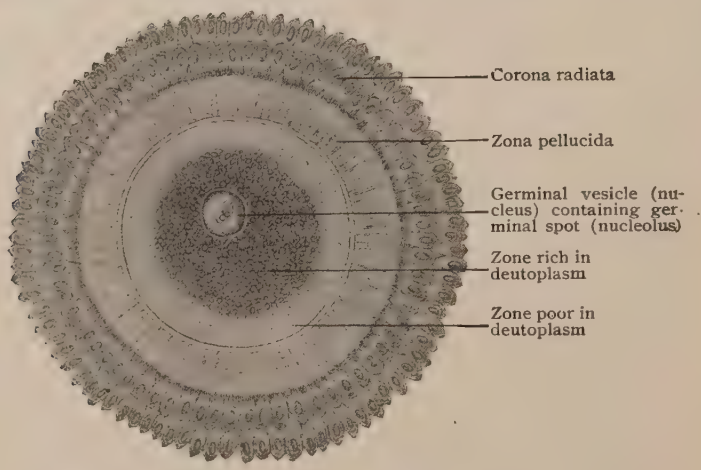


FIG. 12—Human ovum from ripe Graafian follicle. × 160. (*Nagel*).

until finally liberated by rupture of the ovarian tissue. As a cell, the ovum is interesting, since it possesses all parts of the typical cell, including a cell-wall. These parts have long been designated by special names; thus, in the nomenclature of the egg, the cytoplasm is called the **vitellus** or *yolk*, the nucleus the **germinal vesicle,** the nucleolus the **germinal spot,** and the cell-wall the *oölemma*, or **vitelline membrane.** While the ova of birds and reptiles are often of huge size, the yolk of the hen's egg corresponding to a single cell, the true ovum, the mammalian ova are much smaller and barely visible with the unaided eye. The human ovum, when discharged from the ovary, is about .2 millimeter in diameter, spherical in form and composed of cytoplasm containing innumerable yolk-granules. The latter, the representatives of the abundant masses of nutritive material or **deutoplasm** stored as the food-yolk in the bird's egg, are especially numerous in the vicinity of the nucleus. Towards the periphery of the cell they are nearly wanting, a narrow zone of almost homogeneous cytoplasm lying immediately beneath the delicate vitelline membrane. The liberated ovum is surrounded by a

protecting membrane, the *zona pellucida*, which sometimes exhibits a faint radial striation. This envelope is a product of the surrounding epithelial cells lining the little sac, the *Graafian follicle*, enclosing the egg while within the ovary. The large eccentric spherical nucleus, the germinal vesicle, is about 37 μ[1] in diameter and surrounded by a distinct nuclear membrane. Within the germinal vesicle are found the usual constituents of the nucleus, including the all-important chromatin fibrils, nuclear matrix, and nucleolus. The latter, the germinal spot, is distinct and measures about 5 μ in diameter.

The **sperm,** the male germ-cell, is produced by the specialization of epithelial cells lining the seminiferous tubules within the testis. The human sperm consists of three chief parts—the ovoid **head, middle-piece,** which includes the slightly constricted *neck* and the *connecting piece*, and the attenuated and greatly extended **tail.** Although the entire length of the spermatic element is about 50 μ, the head measures only about 5 μ; the male germ-cell, therefore, is much smaller than the ovum. The head and the neck are the most important parts, since they contain respectively the chromatin and the centrosome of the cells, the **spermatids,** from which the sperms are directly derived.

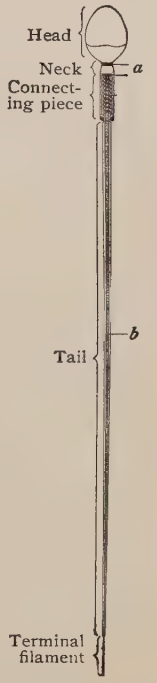


FIG. 13—Diagram of human sperm; *a*, neck-granules, representing the centrosome; *b*, axial fibre. × 1800. (*Meves*).

The centrosome is represented by two minute spherical bodies, the **neck-granules,** which lie in the neck immediately beneath the head and at the anterior extremity of the connecting piece. The **axial fibre** extends throughout the sperm from the neck to the tip of the tail, ending as an attenuated thread, the **terminal filament.** The tail corresponds to a flagellum and serves the purpose of propulsion usually, taking no part in the important changes within the ovum incident to fertilization, during which the head and middle-piece enter the substance of the egg.

Immediately following the construction of a new nucleus from the chromatin contributed by the two parental germ-cells, the fertilized ovum enters upon a cycle of repeated division. As the result of this process, known as **segmentation,** in which the new cells arise by mitotic division, a spherical mass of young cells, the **morula,** is produced. This mass, at first solid, soon acquires a central cavity filled with fluid and is converted into a hollow sphere, known as the **blastodermic vesicle.** The wall of this sac consists of a single layer of cells, except at one place where a small mass of cells is attached to the inner surface. The outer, or covering, layer of cells is the **trophoblast;** the group of cells attached to the inner surface of the trophoblast is the **inner cell-mass.** Corresponding to the position of the latter, the surface of the blastodermic vesicle presents an opaque circular field, the

[1] The sizes of microscopic objects are usually expressed in thousandths of a millimeter, represented by the letter μ; 1 μ (micron) = .001 mm.

embryonic area, so called from the fact that within this area the first traces of the future embryo appear.

In consequence of further growth and differentiation of the inner cell-mass, the latter gives rise to two sheets of cells, the **ectoderm** and the **entoderm.** The first of these is continuous with the trophoblast and, in conjunction with the latter, completes the outer layer of the blastodermic vesicle. The entoderm gradually expands until it forms a complete second layer within and concentric with the outer stratum of the blastodermic wall. Meanwhile a third layer of cells, the **mesoderm,** makes its appearance be-

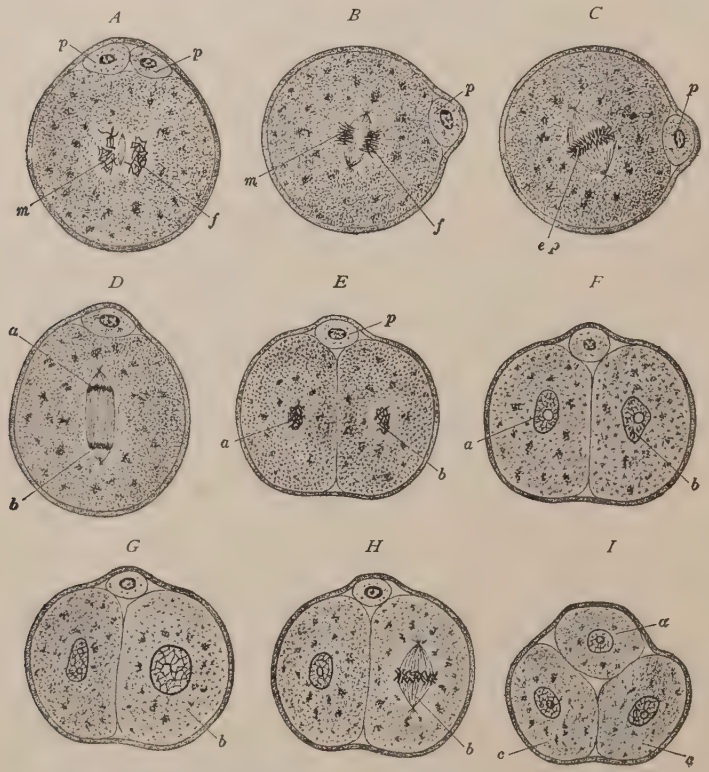


FIG. 14—Early stages of segmentation as seen in sections of ova of mouse. × 450. (*Sobotta.*) *A-D* show the rearrangement of the chromosomes contributed by the male (*m*) and female (*f*) germ-cells as preparatory to the first cleavage of the fertilized ovum; *p*, *p*, polar bodies; *e p*, stage of equatorial plate; *a*, *b*, daughter groups of chromosomes. *E*, *F*, the daughter cells arising from first cleavage. *G*, one cell (*b*) is larger and is preparing to divide. *H*, later stage of this division. *I*, stage of three segmentation spheres (*a* and *c*, *c*) resulting from this division.

tween the ectoderm and the entoderm and, in time, converts the wall of the blastodermic vesicle into a trilaminar envelope. The three cell-sheets derived from the inner cell-mass constitute the **blastodermic** or **germ-layers** —structures of great importance, since they supply the cells from which all parts of the embryo are developed. The histological characters of the outer and inner of these primary layers differ, almost from the first, from those of the mesoderm, their component elements being more compact in arrange-

ment and early acquiring the characteristics of covering cells or epithelium.

The mesodermic elements, on the contrary, for the most part assume irregular forms and are loosely held together by intercellular substance, thus foreshadowing the features which distinguish many of their derivatives as members of the connective tissue group.

The mesoderm undergoes important modifications, splitting into two

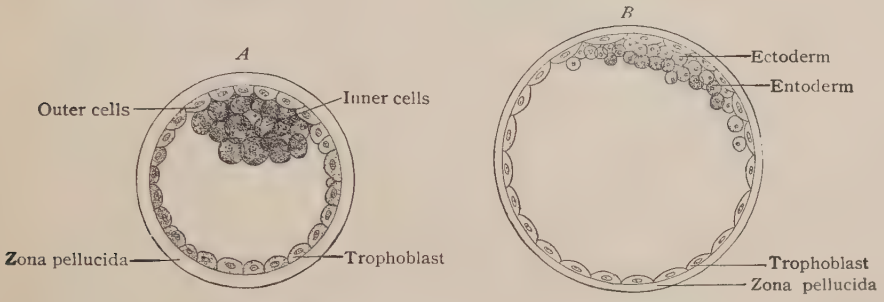


FIG. 15—Diagrams of very early stages of the mammalian blastodermic vesicle; *A*, the vesicle consists of trophoblast and inner cell-mass; *B*, the inner cell-mass is differentiating into ectoderm and entoderm. (*After van Beneden.*)

sheets, a **parietal** and a **visceral layer,** between which is included the primitive body-cavity, or **cœlom.** Subsequently this space is subdivided into the great serous sacs of the body—the pericardial, the pleural, and the peritoneal —lined with the modified mesodermic elements, known as **mesothelium.** The cleavage of the middle germ-layer, however, does not involve the meso-

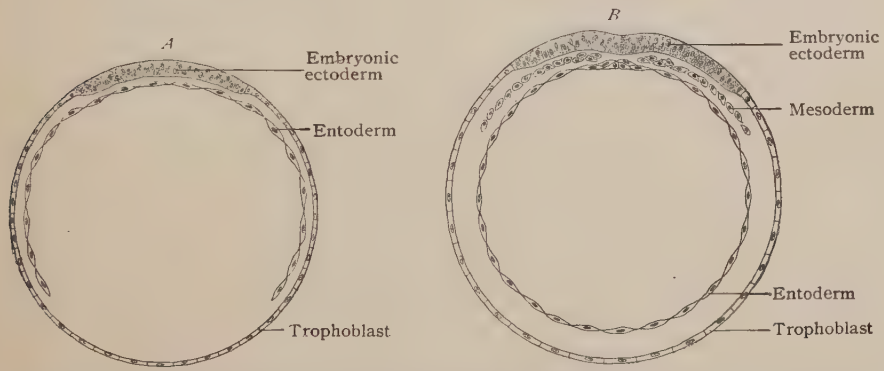


FIG. 16—Diagrams of later stages of the mammalian blastodermic vesicle; *A*, the thickened embryonic ectoderm corresponds to the area in which the embryo will develop; *B*, the mesoderm is appearing as the third germ-layer between the ectoderm and the entoderm, the latter now forming a complete layer.

derm in the immediate vicinity of the embryonic axis, since on each side of the latter there remains a tract of uncleft **paraxial mesoderm,** in which appears a series of quadrilateral areas, the **mesodermic somites.** These are important since they contribute the material giving rise to the vertebral column and the voluntary muscles.

The parietal layer of the mesoderm adheres to the ectoderm and, in conjunction with the latter, constitutes the **somatopleure,** the ecto-mesodermic sheet that forms the ventrolateral walls of the body. In like

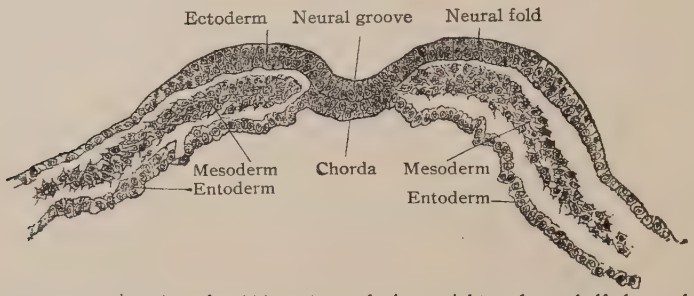


FIG. 17—Transverse section of rabbit embryo of about eight and one-half days, showing the character of the early germ-layers; the future neural canal is represented by the widely open groove. × 80.

manner, the visceral layer adheres to the entoderm and, with it, constitutes the **splanchnopleure,** whose folding-off establishes the digestive tube.

Since these primary layers give rise to all the tissues of the body, a synopsis of their genetic relations may be given; a word of caution, however, should be added against regarding these groups as too sharply defined, since a certain degree of transition must be recognized.

DERIVATIVES OF THE BLASTODERMIC LAYERS

From the ectoderm are derived:

Epithelium of outer surface of the body, including that of the conjunctiva and anterior surface of the cornea, and of the external auditory canal, together with the epithelial appendages of the skin, as hairs, nails, mammary, sebaceous and sweat-glands (including the involuntary muscle of the latter).

Epithelium of the nasal fossa, with its glands, as well as the accessory nasal sinuses.

Epithelium of the mouth and of the salivary and other glands opening into the oral cavity.

Enamel of the teeth.

Tissues of the nervous system, including neurones, neuroglia, ependyma and epithelium of the choroid plexuses.

The retina; the crystalline lens, suspensory ligaments of lens, and perhaps part of the vitreous humor; the sphincter and dilatator muscles of the iris.

Epithelium lining the membranous labyrinth.

Epithelium of the hypophysis and of the pineal body.

Glandular epithelium of medulla of adrenal.

From the mesoderm are derived:

Connective tissues, including areolar tissue, tendon, ligaments, cartilage, bone, dentine, and fat.

Muscular tissue, except that of the sweat-glands and iris.

Tissues of the vascular and lymphatic systems, including their endothelium and circulating cells.

All parts of the sexual glands and their excretory passages, as far as the termination of the ejaculatory ducts and of the vagina.

All parts of the kidney and ureter.

Glandular epithelium of cortex of adrenal.

From the entoderm are derived:

Epithelium of the digestive tract, with that of all glandular appendages, except those portions of ectodermic origin at the beginning (oral cavity) and termination of the tube.

Epithelium of the respiratory tract.

Epithelium of the urinary bladder and of urethra (except part of male).

Epithelium of prostate and Cowper's glands.

Epithelium of thyroid, parathyroid, and thymus bodies.

THE ELEMENTARY TISSUES

When we examine the various parts and organs of the body, we find that the distinctive tissues of which they are composed may be classified, according to their structure, into four fundamental groups of **elementary tissues**—the **epithelial,** the **connective,** the **muscular,** and the **nervous.** By the association and modification of two or more of these tissues the organs are made up and acquire the distinctive characteristics demanded by their function. A fifth group—the **fluid tissues,** including the blood and lymph—is sometimes added in view of the liquid character of the intercellular substance of these tissues. Genetically, however, these are closely related with the connective tissue group, and if they are regarded as elementary tissues, may be classed with the connective tissues.

THE EPITHELIAL TISSUES

The epithelial tissues include, primarily, the sheet of protecting cells (epidermis) covering the exterior of the body and the epithelium lining the digestive tube. Secondarily, they constitute the derivations of the epidermis, as hairs, nails, glands of the skin, the lining of the ducts and compartments of the glands connected with the digestive canal, and the lining of the respiratory tract, which originates as an evagination from the gut-tube. Further, epithelium forms the lining of the genito-urinary tract.

The primary purpose of the epithelium being to protect the delicate vascular and nervous structures lying within the subjacent connective tissue of the skin and of the mucous membranes, the epithelial cells are arranged as a continuous sheet, the individual elements being united by a very small amount of intercellular, or cement, substance.

Epithelium is devoid of blood-vessels, the necessary nutrition of the tissue being maintained by the absorption of nutritive fluids from the vascular connective tissue with which it is in contact. The distribution of nerve-fibres within epithelium ordinarily is scanty, although in localities possessing a high degree of pain sensibility, as the surface of the cornea, the terminal nerve-filaments may lie between the epithelial elements. Frequently the epithelium is separated from the connective tissue upon which it rests by a delicate *basement membrane,* or **membrana propria.** The latter usually appears as a linear subepithelial boundary, being often particularly well marked beneath the epithelium of glands.

Based on the predominating form of the component cells, the epithelial tissues are divided into two chief groups, **squamous** and **columnar,** each of which is subdivided into **simple** and **stratified,** according to the presence of a single or several layers of cells respectively. **Modified epithelium** includes cells which exhibit adaptation and specialization to meet particular uses; such are the ciliated, pigmented, and glandular epithelia. Highly differentiated **neuro-epithelium** occurs in the perceptive apparatus concerned in the

special senses, the gustatory cells of the taste-buds found on the tongue, the rod- and cone-cells of the retina, and the auditory cells of Corti's organ being familiar examples.

Squamous Epithelium.—Where this variety of epithelial tissue occurs as a single layer, it is called **simple squamous** epithelium and consists of flattened nucleated cells, which are in contact with one another along their margins, and when viewed from the surface, form a more or less regular mosaic. Hence the terms "pavement" or "tessellated" are sometimes applied to this type of epithelium. Such arrangement of the squamous type is seen in the lungs, lining the terminal air-spaces, and in the kidney, within the capsule of the renal corpuscles, and in the descending limb of the medullary loops of the renal tubules. It also lines the greater part of the membranous labyrinth of the internal ear.

The more usual disposition of the squamous type of epithelium is as a number of superimposed layers, this constituting the important group of

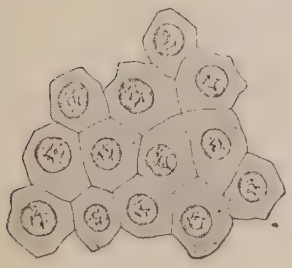


FIG. 18—Simple squamous epithelium from the anterior capsule of the crystalline lens. × 360.

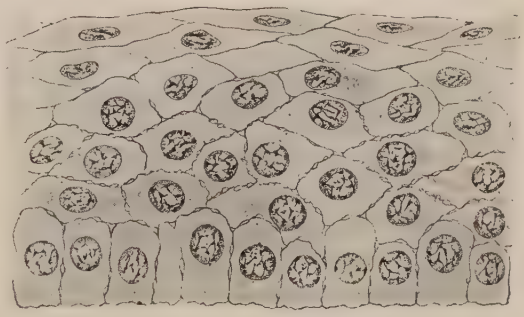


FIG. 19—Stratified squamous epithelium from anterior surface of the cornea. × 465.

stratified squamous epithelium. Although the free surface of such structures is formed of typical scale-like cells, the entire tissue is by no means composed of flattened cells. When seen in section (Fig. 19), the deepest cells are not squamous, but irregularly columnar, resting on the basement membrane by slightly expanded bases. The surface of the underlying connective tissue is often raised into minute elevations or papillæ, which serve as advantageous positions for loops of capillary blood-vessels and terminations of nerves. Good examples of such papillæ are seen in the skin and in the œsophagus. This increased area of contact between the epithelium and the underlying connective tissue is not only a useful nutritional device, allowing more epithelial cells direct relation with the vascularized tissues, but also a mechanical device because of the interlocking of the two tissues. This latter is important in surfaces exposed to hard objects, which cause mechanical strains and shears. Owing to the more favored nutrition of the deepest stratum, the cells next the connective tissue possess the greatest vitality and are the source of the new elements necessary to replace the old cells which are continually being removed at the free surface. This loss is due

not only to mechanical abrasion, but also to the displacement of the superficial elements by the new cells formed within the deeper layers.

Passing from the basement membrane towards the free surface, the form of the cells undergoes a radical change. The columnar type belongs exclusively to the deepest layer; the superimposed cells assume irregularly polyhedral forms and gradually expand parallel to the free surface, to become, finally, the large thin scales (Fig. 20) so characteristic of the superficial layers of stratified squamous epithelium. The shape of the nucleus also varies with the situation of the cells, since within those next the basement membrane the nucleus tends to be oval, with its long axis vertical, while within the cells of the middle layers it is spherical, and in the superficial strata the nucleus becomes more and more flattened, with its long axis horizontal. The irregularly polyhedral cells of the deeper strata frequently are connected by delicate protoplasmic processes which bridge the intervening intercellular clefts (Fig. 21); when such elements are isolated, the

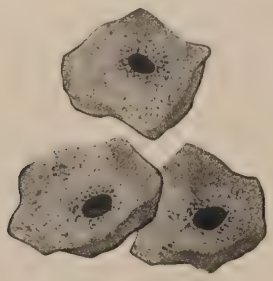


FIG. 20—Isolated surface cells from epithelium lining the mouth. × 320.

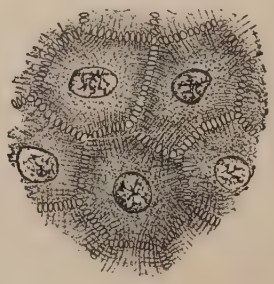


FIG. 21—Epithelial cells from epidermis, showing intercellular bridges. × 675.

delicate connecting threads are broken and appear as minute spines besetting the so-called **prickle cells.** The cells of the several different layers have different physical properties, as shown by the microdissection of living cells of the human epidermis (Chambers and Rényi, '25). They find that the cells of the superficial layers are easily isolated and are tough and horny. Cells of the deeper layers are firmly bound together, being joined by numerous cytoplasmic bridges. When torn apart they are seen to be polyhedral, with rounded corners. Their substance is softer than that of the superficial squamous cells, but still is a tough and non-adhesive jelly. The individual cell can be stretched slightly with needles, and the wrinkles produced by the stretching disappear very slowly when the cell is set free. The cytoplasm is optically structureless except for a few conspicuous granules. The nucleus is a translucent oval body rather firmly embedded in the highly gelatinous cytoplasm. With a needle it may be displaced slightly, but when the pressure is released it moves back to its original position. The fluid condition of the nucleus is indicated by the fact that an indentation of the nuclear membrane produced by the pressure of the needle quickly disappears when the pressure is removed. The nucleus is irreparably injured by a puncture of its membrane and rapidly sets into a jelly with a coarse reticular structure.

Another type of stratified epithelium is that called **transitional,** found in the lining of the urinary tract (renal pelvis, ureter, urinary bladder, and beginning of urethra). In the distended bladder the epithelial layer is thinner than in the collapsed organ, and there is a change of shape of all the constituent cells. There are usually four to six layers of cells, and the most characteristic cells are those forming the free surface. In the distended condition the superficial cells are flattened, though not as thin as in typical stratified squamous epithelium. In the collapsed condition the superficial cells are more globular, often with somewhat rounded upper surfaces. In both conditions these superficial cells extend over several of the subjacent cells, and their lower surfaces fit closely into the depressions between the smaller adjoining cells. When the larger superficial cells are examined separately, their cytoplasm is found to be tough and only

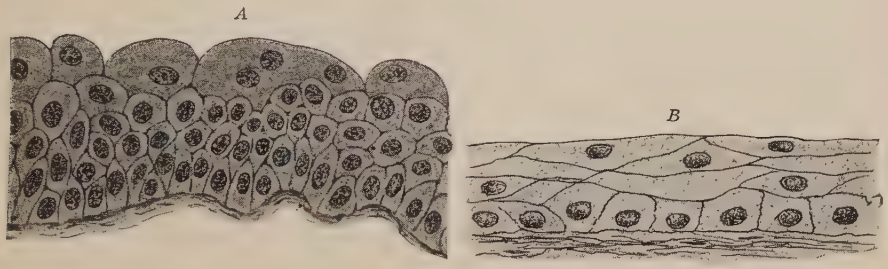


FIG. 22—Transitional epithelium from the bladder. *A*—Collapsed condition. *B*—Distended condition.

slightly elastic, so that they retain the impressions of the cells with which they were originally in contact (Fig. 22).

The transitional epithelium differs from ordinary stratified squamous epithelium also in having no protoplasmic bridges. When pulled apart there is seen a delicate intercellular slimy substance. This, no doubt, acts as a cement-substance, and allows more readily the change in form of the cells incident to the distended and collapsed conditions of the bladder.

Columnar Epithelium.—When consisting of a single layer of prismoidal elements, the epithelium constitutes the **simple columnar** variety. This is more widely distributed than the simple squamous group, and is seen in the lining of the stomach, of the intestinal tube, of the gall-bladder, of the ducts of glands, and in other localities. When the single layer of cells is replaced by several, as in the **stratified columnar** epithelium, the superficial elements alone are typically columnar. The free ends of the prismoidal cells frequently present cytoplastic specializations in the form of a **cuticular border,** while their ends which rest upon the basement membrane are pointed, club-shaped, or forked. The intervals formed by such irregular contours are occupied by the smaller cells of the deeper stratum. Each cell is provided with a nucleus, which is situated about the middle within the superficial elements and nearer the base within the deeper ones. The cytoplasm of the columnar epithelial cells of the intestine is a soft highly viscid jelly, which by microdissection methods can be pulled out into

long strands. When the cell is injured, its nucleus becomes coagulated and the cytoplasm changes in consistency, so that on being torn with needles, it breaks into non-viscid pieces. The cuticular border is a definite, comparatively stiff structure which is more or less continuous from cell to cell. There are no intercellular bridges, and adjoining cells are more definitely adherent to one another at the cuticular border than elsewhere.

Modified Epithelium.—In order to meet particular work, beyond the mere function of covering and of protection, epithelial cells may undergo profound modification or high specialization. Thus, in order to produce a current favorable for the propulsion of mucus or secretions, the free surface of the columnar epithelium in many localities, as in the trachea and bronchial tubes, the inferior and middle nasal meatuses, the oviducts and uterus, is provided with minute hair-like vibratile processes, or **cilia.** These hair-like processes attached to the free surface are continuous with delicate intracellular fibrillæ within the superficial parts of the cells. The number of cilia attached to each cell varies, but there are usually between one and two dozen such appendages. Their length, likewise, differs, those lining the

FIG. 23—Simple columnar epithelium and goblet-cells from epithelium lining large intestine. × 500.

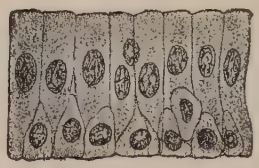


FIG. 24—Stratified columnar epithelium from vas deferens. × 500.

epididymis being about ten times longer than those attached to the trachea mucous membrane. Under favorable conditions, including a sufficient supply of moisture, oxygen, and heat, ciliary motion may continue for many hours or even days after removal of the tissue.

The cytoplasm of epithelial cells sometimes contains particles which are colored and composed of melanin. Such cells acquire a dark-brown tint and are then known as **pigmented epithelium.** Examples of such cells are seen in the outer layer of the retina and in deep cells of the epidermis in certain races.

On surfaces clothed with columnar epithelium, many cells are distinguished by unusually clear cytoplasm and exceptional form and size. These are the **goblet-cells,** whose peculiar chalice-form results from an accumulation of mucoid secretion elaborated within the cytoplasm of the cells. When distention becomes too great, the cell ruptures in the direction of least resistance and the secretion is poured out upon the surface of the mucous membrane as the lubricating mucus. The goblet-cells, therefore, may be regarded as unicellular glands and as representing a simple phase in the specialization of glandular tissue. When groups of epithelial elements become permanently modified to engage in the elaboration of secretions, they are recognized as **glandular epithelium.** The cells lining the ducts and

the ultimate compartments of the glands are all extensions of the epithelium covering the adjoining mucous membrane. Within secreting cells, there are usually demonstrable the **secretory granules** and **globules**, which are the immediate antecedents of the specific secretion. These granules and globules are of plastic and transitory nature, and vary in number and size at different stages of the secretory cycle. Just prior to their discharge, they form conspicuous elements within the cytoplasm, as the mass of mucus in goblet-cells, the zymogen granules in the pancreatic cells, and the milk-globules in the mammary cells.

The highest and most complex modifications of epithelial tissues are

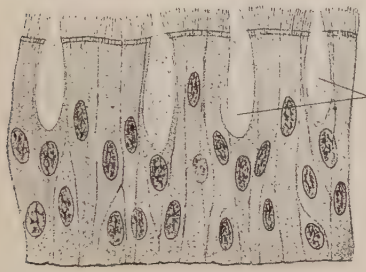


FIG. 25—Stratified ciliated columnar epithelium from trachea. × 500.

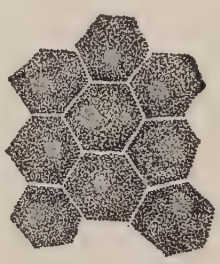


FIG. 26—Pigmented epithelium from the human retina, unstained. × 435.

those occurring during the development of the structures designed to receive the stimuli giving rise to the special senses. The epithelium in these localities is differentiated into two groups of elements, the sustentacular and the receptive; to the latter the name of **neuro-epithelium** is applied. Conspicuous examples of such specialized epithelium are the rod- and cone-cells of the retina and the auditory or hair-cells of Corti's organ in the internal ear.

A more detailed description of glandular epithelium is given in the chapter devoted to Mucous Membranes and Glands; the details of the neuro-epithelial structures are included under the appropriate Organs of the Senses.

ENDOTHELIUM AND MESOTHELIUM

The term endothelium in its widest sense is applied to the modified mesodermic cells that cover serous surfaces anywhere within the body, as well as those lining blood- and lymph-vessels. It is now usually restricted to the lining of the blood-circulatory and lymphatic systems, and of small spaces such as the anterior chamber of the eye, while the term mesothelium includes the lining of the pericardial, pleural, and peritoneal subdivisions of the body-cavity. In development, these spaces are intramesodermic clefts and the elements forming their lining are derivatives of the great connective tissue producing germ-layer. The endothelium and mesothelium, therefore, are closely related to the connective tissues and, in a sense, may be regarded as modified elements of that class. In view of their arrangement as investing cell-sheets and other resemblances, they may be conveniently discussed in connection with the epithelial tissues; indeed, up to the time of the intro-

duction of the term endothelium by His in 1865 they were always regarded as epithelia, and they are still so regarded by many histologists.

The most striking difference in situation between the endothelia and the epithelia is the fact of the former covering surfaces not communicating with the atmosphere, while the epithelial tissues clothe mucous membranes, all of which are directly or indirectly continuous with the integumentary surface. A further though incomplete contrast between these tissues is presented in their genetic relations with the germ-layers, since the epithelia, with certain exceptions which are derived from the mesoderm, are transformations and outgrowths from the ectoderm and entoderm, while the endothelia are all direct modifications of mesodermic cells.

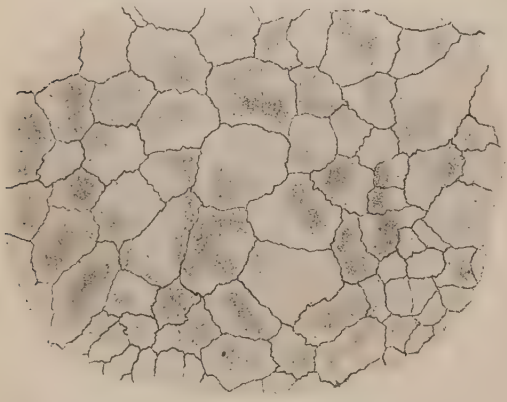


FIG. 27—Mesothelial cells from surface of omentum; intercellular cement-substance stained by silver nitrate. × 300.

As seen in typical preparations, obtained from the peritoneum after appropriate treatment with silver nitrate, the mesothelial cells on surface view appear as irregularly polygonal areas mapped out by deeply tinted lines (Fig. 27). The latter represent the silver-stained albuminous intercellular cement-substance, which joins the flattened cells in a manner similar to that seen in simple squamous epithelium. The lines of apposition are sinuous and less regular than those between epithelial cells, in many cases the lines appearing distinctly serrated. The form of the cells and the character of their contours, however, are not constant, since they are greatly influenced by the degree of tension to which the tissue has been subjected. The cells are very susceptible to injury during microdissection and quickly disintegrate if torn. By traction on adjoining cells they are easily separated except at the corners where several cells meet.

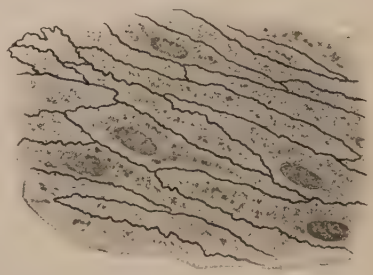


FIG. 28—Endothelial cells lining artery of dog: stained with silver and hematoxylin. × 450.

THE CONNECTIVE TISSUES

The important group of connective substances, the most widely distributed of all tissues, is the direct product of the middle germ-layer. Since the latter is also the origin of some epithelial, most muscular, and all vascular and lymphoid tissues, that portion of the mesoderm especially concerned in

producing the connective tissues has been designated the **mesenchyma.** Their essential rôle, connection, and support, being largely passive and mechanical, the physical characteristics of these tissues are of much importance. These depend upon the intercellular substance, which, in marked contrast to the meagre cement-substance of the epithelia, is usually large in amount and contributes the chief bulk of the tissue.

During the period of embryonal growth the intercellular substance is semi-fluid, gelatinous, and plastic; a little later, as growing connective tissue, it is still soft, although more definitely formed; while, as the adult areolar tissue, it becomes tough yet pliable. Grouped as masses in which fibrous tissue predominates, the intercellular substance acquires the toughness and inextensibility of tendon; where, on the contrary, large quantities of elastic tissue are present, as in certain ligaments, extensibility is conspicuous. Further condensation of the intercellular substance produces the firmness encountered in hyaline cartilage, intermediate degrees of condensation being presented by the fibrous and elastic varieties of cartilage. In those cases in which the ground-substance becomes impregnated with calcareous salts, the hardness of bone or of dentine results. Notwithstanding these variations in the density and physical properties of the intercellular substance, the cellular elements have undergone relatively little change, whether found in fibrous connective tissue, cartilage, or bone.

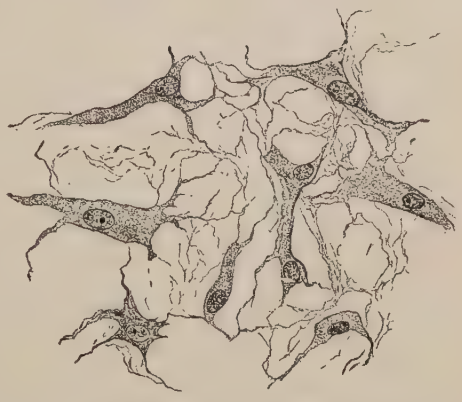


FIG. 29—Embryonal connective tissue from section of very young umbilical cord. × 350.

The principal forms in which connective tissue occurs are: (1) **Embryonal Connective Tissue,** or **Mucous Tissue,** (2) **Reticular Tissue,** (3) **Fibrous Tissue**—loose and dense, (4) **Adipose Tissue,** (5) **Cartilage,** and (6) **Bone.**

Embryonal Connective Tissue.—This form of connective substance is the most immature and closely resembles the parent tissue, the mesenchyma. As seen in sections of the embryo, or of the early umbilical cord, it consists of a delicate protoplasmic network containing a semi-fluid intercellular substance. The network is formed by the close approximation of the processes of irregularly branched stellate or fusiform cells, whose oval nuclei are embedded in plate-like masses of faintly granular cytoplasm (W. H. Lewis, '22). The intercellular ground-substance is semi-fluid and, depending upon the stage of development, either structureless or traversed by indistinct fibres. Being essentially embryonal tissue, it is limited to the earlier stages of development. It forms the so-called **jelly of Wharton** in the umbilical cord, and a study of the latter at different stages shows the change in relative proportions of cells and intercellular substance with increasing age, and also the growth of the fibrous component of the intercellular

substance. At present there are two main theories regarding the mode of formation of connective tissue fibres—the intercellular theory and the intracellular theory. In both, the cells are regarded as the ultimate source of the material from which the fibres are formed.

According to the intercellular theory the amorphous gelatinous ground-substance is formed as a secretion of the cells. Under the influence of chemical and mechanical factors the connective tissue fibrils develop in it through a consolidation of its colloidal constituents. This has been directly observed in amphibian embryos (Baitsell, '21).

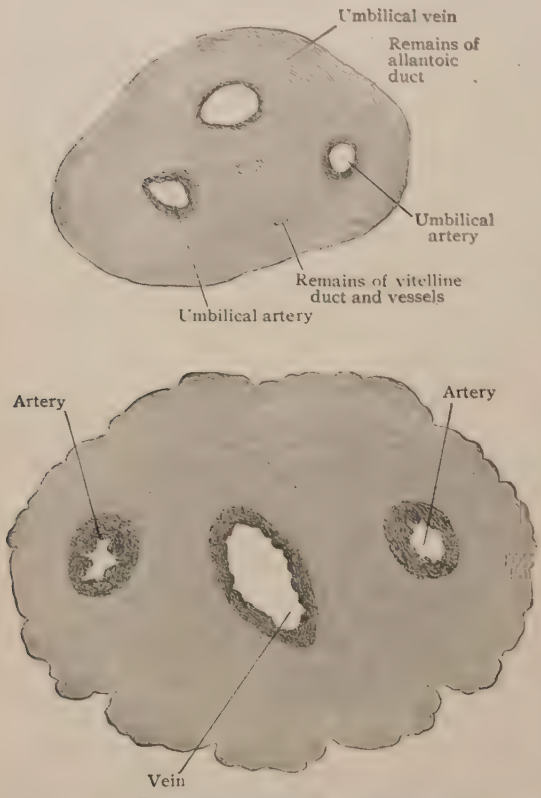


FIG. 30—*A*, Transverse section of umbilical cord of third month. × 12; *B*, Transverse section of umbilical cord at end of pregnancy, taken from placental end; the umbilical blood-vessels are embedded within the embryonal connective tissue. × 10.

According to the intracellular theory, strands appear within the peripheral cytoplasm. These strands gradually separate from the cell to become the fibres.

Reticular Tissue.—This variety of connective tissue is, in some ways, the least differentiated from the embryonal type. It consists chiefly—in some instances almost exclusively—of a network of branching connective tissue cells, the meshes of which are occupied by the fluid and the lymphoid and other cellular elements which the reticulum supports. In connection with the cells are usually developed very delicate fibres, which, however, form the less conspicuous part of the tissue. The reticular fibres probably differ somewhat from the white fibres of connective tissue in chemical composition, containing a variety of gelatin known as **reticulin.** Reticular tissue occurs as the supporting framework of lymphoid tissue, hence is well seen in suitably prepared sections of the lymph-nodes and of the spleen. It forms the framework of bone-marrow, and is also found in the mucous membrane of the intestinal tract, and in the interstitial tissue of certain organs, as the kidneys and liver. The reticulum cells are phagocytic, and form an important part of the reticulo-endothelial system of Aschoff.

Fibrous Tissue.—Under this head are included the more usual forms of connective tissue which have representation in, practically, all parts of the body. They exhibit a wide range of variation in their physical proper-

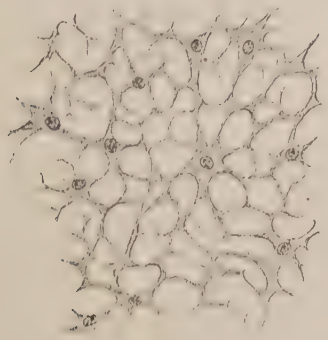


FIG. 31—Reticular tissue from lymph-node. × 300.

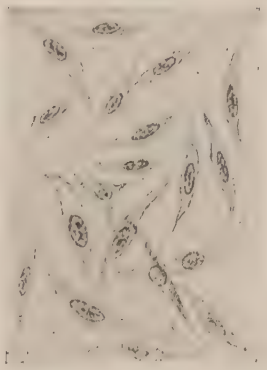


FIG. 32—Young connective tissue cells (fibroblasts) from subcutaneous tissue of cat embryo. × 590.

ties which depend upon differences in the intercellular substance, due to modifications in the arrangement and proportions of its constituents. Before considering the several varieties of fibrous connective tissue, loose and dense,

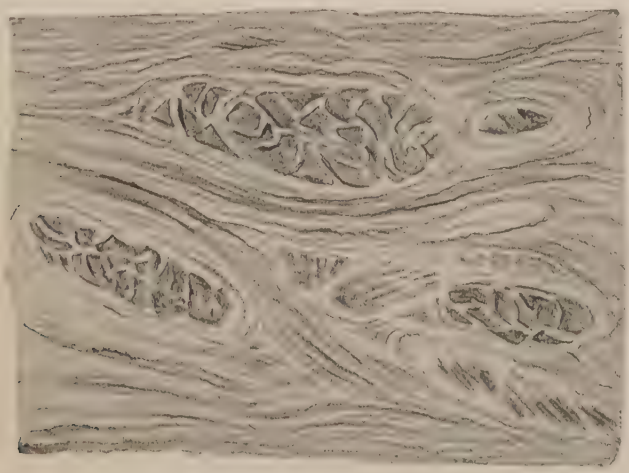


FIG. 33—Subcutaneous fibrous connective tissue, to show bundles cut in various directions.

the histological components common to all these tissues claim attention. These components are the **cells** and the **fibres.**

Connective Tissue Cells.—Although the more active constituent of the connective tissue, it is only in the younger stages that the cells are conspicuous; later, after the tissue has acquired its definite characteristics, the intercellular substance has usually become so predominant that the cells

are reduced to inconspicuous elements, notwithstanding their important rôle as nutritive and reproductive centres. The irregularly branched or stellate types of the parent mesenchymal cells are retained ordinarily only during the earlier periods of growth, the connective tissue cells decreasing in prominence as the intercellular substance increases in amount and differentiates into definite bundles of fibres. In the adult tissues, with few exceptions, the cells appear as small fusiform or flattened elements, in which the deeply staining oval nucleus, surrounded by a small amount of cytoplasm, serves as the chief means of detection. Being thicker than the cell-body, the nucleus projects beyond the general level of the cell and, viewed in profile, appears as a colored linear elevation embedded in a plate of faintly tinged cytoplasm. The cells are bathed by the tissue-fluids which exist everywhere between the bundles of fibrous tissue. Where the latter are closely packed, the juice-channels form a series of intercommunicating spaces or canals. This is well demonstrated in dense fibrous tissue after staining with silver nitrate, when the spaces appear as light, irregularly stellate figures (Fig. 34), in which are lodged the connective tissue cells. In principle, the same arrangement holds good for cartilage and bone, since in these tissues the cells lie within the **lacunæ**, the spaces within the intercellular matrix. The connective tissue cells, when subjected to thermal, chemical, or electrical stimulus, exhibit changes in form, possessing the power of retracting their processes and displaying amœboid movement.

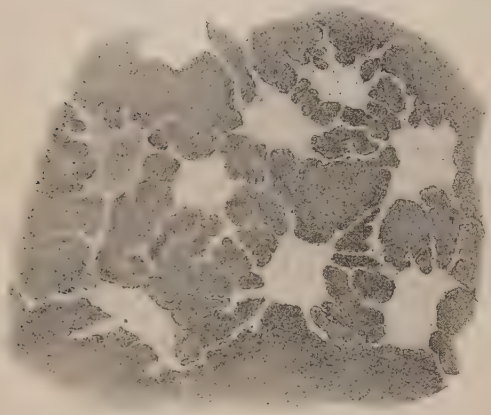


FIG. 34—Tissue-spaces within dense connective tissue, from cornea of calf; the surrounding ground-substance has been stained with silver nitrate. × 500.

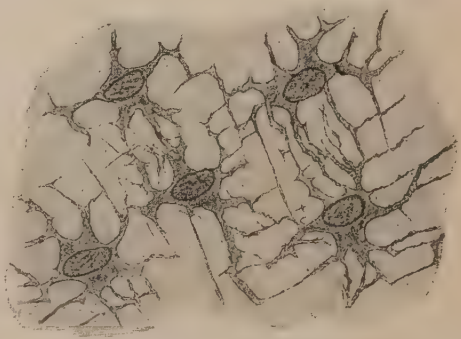


FIG. 35—Connective tissue cells, from cornea of calf, which occupy spaces similar to those shown in preceding figure. ×525.

In a few localities in man—the choroid, the iris, the sclera, the dermis, and the pia mater—the connective tissue elements often contain dark particles of **melanin** and, therefore, appear as conspicuous irregular figures shading from brown to black. Such elements are usually spoken of as **connective tissue pigment cells,** being connective tissue cells modified by the presence of the colored material. Since this invasion is limited to the cytoplasm, the

unaffected nucleus appears in unstained preparations as a small, light, oval area in the midst of the dark figure (Fig. 36). At times the connective tissue cells take up colored material derived from the blood and thus contain blood-pigment. In addition to the melanin series and the hemoglobin derivatives, a third group of pigments, the **lipochromes,** is derived from fat. A very common modification of the connective tissue element is the appearance of droplets of oil within its cytoplasm. When such invasion becomes extensive, the element becomes a **fat cell** and a constituent of adipose tissue.

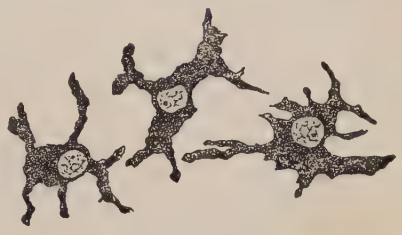


FIG. 36—Pigmented connective tissue cells from choroid. ×400.

In addition to the characteristic **fixed connective tissue cells** and their modifications containing pigment and fat, a variable number of **free cells** are encountered in the less dense forms of fibrous tissue. The most constant of these free cells are the **migratory lymphocytes,** which escape from the blood-vessels into the clefts between the bundles of fibres. They appear as small irregular cells in which the spherical deeply stained nucleus is surrounded by a narrow zone of cytoplasm. The lymphocytes change their position by amœboid movement. The rate of progression of lymphocytes of the blood, as found by continuous observation of these cells at body-temperature varies from 4 μ per minute in the first hour to 15 μ in the ninth (McCutcheon, '24). The maximal rate is 30 μ per minute, approaching the speed of a neutrophilic leucocyte. The nucleus lies in the front part of a moving cell. Occasionally larger elements with the general characters of lymphocytes, the **plasma-cells,** are seen. They are probably derived from the lymphocytes, but differ from these in their larger size, greater amount of readily staining cytoplasm, and eccentric nucleus. Their cytoplasm stains deeply with basic dyes and their nuclei show the chromatin particles arranged peripherally in large clumps. Two other forms of free cells, the **tissue mast-cells,** and the **eosinophiles,** are conspicuous by reason of the coarse granules with which their cytoplasm is laden. The **tissue mast-cells** are irregularly round or oval in shape and possess an oval nucleus (Fig. 37). The coarse granules are deeply colored by basic dyes. The **eosinophiles** are distinguished by granules which possess an especial affinity for eosin and other acid dyes. Under the name **clasmatocytes,** are described irregular branched cells with long processes which are highly phagocytic. **Neutrophilic leucocytes** are seen in small numbers under

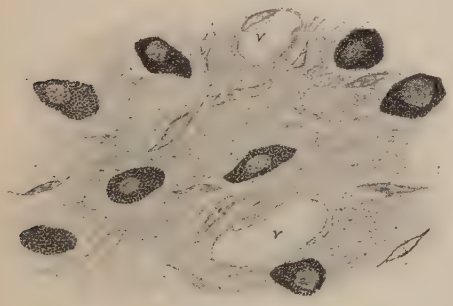


FIG. 37—Mast-cells from submucous tissue of mouth; *v,v,* blood vessels. × 825.

normal conditions, but appear in great numbers in inflammation. Their rate of progression, as seen in vitro in whole blood, has been found to average 34.1 μ per minute (McCutcheon, '23). The rate shown by different cells varied from 18 μ to 47.4 μ per minute.

Connective Tissue Fibres.—The intercellular substance of fibrous connective tissue includes two varieties of fibrillar constituents, the **white fibres** and the **elastic fibres.**

The **white,** or *collagenous*, **fibres** are grouped in more or less definite bundles, which as seen in the usual teased preparations of areolar tissue, exhibit a wavy longitudinal striation. This marking is due to the apposition of the individual fibrillæ, which are so thin as to have no appreciable width. In the denser forms of fibrous tissue, as in tendon, the white fibres are

FIG. 38—Teased preparation of subcutaneous tissue, showing constituents of areolar tissue. × 300.

assembled in robust fasciculi with great regularity and so closely packed and luted together by cement-substance that all trace of the individual fibrillæ is lost, the bundle appearing homogeneous, unless some means is taken to dissociate its component fibrils. White fibres yield gelatin on boiling with water, and consist chemically of an albuminoid substance termed **collagen.** They are not digested by pancreatin, and on the addition of acetic acid, become swollen and transparent, and, finally invisible.

The **elastic fibres** usually occur as networks of highly refracting homogeneous fibrils which lie among the bundles of white fibres. The individual fibres are much thicker than the white ones and, although differing in width maintain a constant diameter until augmented by fusion with other elastic fibres. So long as the tissue in which they lie maintains its normal tension, the elastic fibres remain taut and approximately straight, but when dissociated, as in teased preparations, they assume a characteristic form and

become wavy, bowed, or coiled. The proportion of elastic fibres in fibrous connective tissue is, ordinarily, small, conferring only a moderate degree of elasticity. In certain localities, however, as in the ligamenta flava of man

FIG. 39—Endocardium, with subjacent myocardium; connective tissue blue and heart muscle red, as in Mallory's aniline blue and acid fuchsin stain. ×70.

and the ligamentum nuchæ of quadrupeds, almost the entire structure is made up of robust elastic fibres, held together by a small amount of intervening white fibres. In transverse sections of such ligaments (Fig. 41), the individual elastic fibres appear as minute polygonal areas, separated by the white fibres and the associated connective tissue cells. Where, on the other hand, elasticity would be disadvantageous, as in tendons

FIG. 40—Portions of isolated elastic fibres from ligamentum nuchæ of ox. × 375.

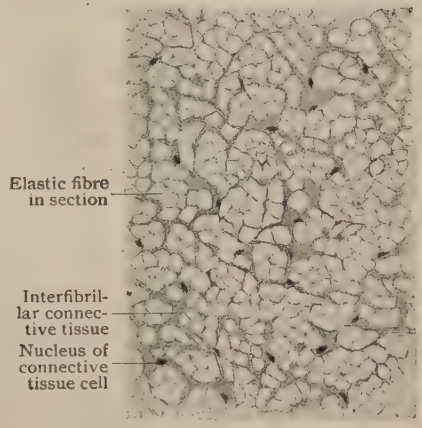


FIG. 41—Transverse section of ligamentum nuchæ of ox. × 450.

and aponeuroses, very few elastic fibres are present, the dense fibrous structures being composed practically of white fibres alone. Within the walls of the larger blood-vessels, the elastic fibres are numerous, and in the internal and external elastic laminæ are arranged into especially close networks. Elastic fibres withstand dilute acids and alkalies, consequently becoming more evident in tissue treated with acetic acid in which the white fibres disappear. In their chemical composition they differ from the white fibres, yielding **elastin** and not gelatin on boiling and disappearing upon being subjected to pancreatic digestion. Likewise, in their staining reactions, elastic fibres differ from the white; by taking advantage of the affinity which the former possess for certain dyes, as basic fuchsin and orcein, a much wider and more generous distribution of elastic tissue has been established than was formerly appreciated.

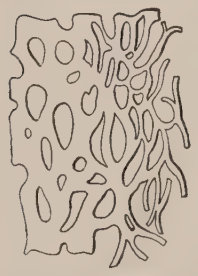


FIG. 42—Fragment of fenestrated membrane from large artery; surface view. × 510.

Loose fibrous, or **areolar, tissue** occurs throughout the body wherever the opposed parts, although connected, enjoy considerable mobility. Familiar examples are the sheets or tracts of yielding connective tissue, which lie between the skin and underlying fascia or beneath mucous membranes,

FIG. 43—Portion of omentum, showing fibro-elastic tissue arranged as a fenestrated membrane; the nuclei belong to the connective tissue and surface mesothelial cells. × 120.

FIG. 44—Longitudinal section of tendon from young subject; the tendon-cells are seen in profile between the primary bundles of fibrous tissue. ×300.

that unite the muscles and assist in keeping the viscera in place. The variable bundles of white fibres are loosely and irregularly disposed, crossing in all directions and enclosing correspondingly irregular clefts. The elastic fibres form a network of highly refracting threads which, in sections and teased preparations, are more or less wavy and curled. The cellular con-

stituents of the normal tissue are relatively inconspicuous, but here and there the fixed connective tissue cells are seen as spindle-shaped or irregular plate-like bodies and the free cells usually as rounded forms. In the interfascicular spaces are the tissue-fluids, and in this fluid the free cells migrate about under various chemotactic influences. In inflammatory reactions great numbers of cells appear in the clefts of the areolar tissue, coming mostly from nearby capillaries. Areolar tissue forms the supporting medium for blood-vessels, nerves, and lymphatics; and the process of dissection is largely taken up with the removal of areolar tissue.

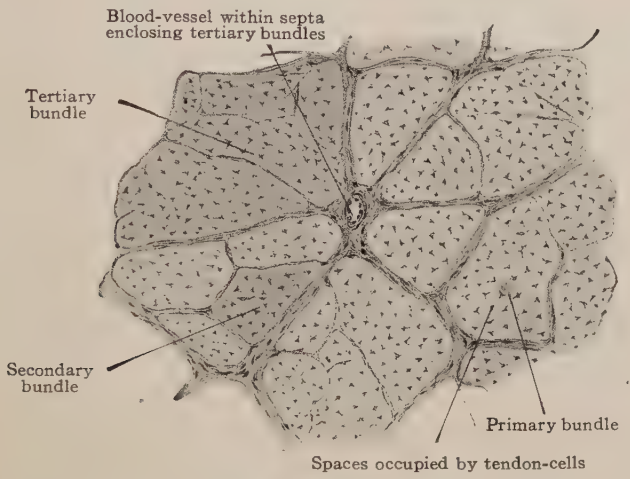


FIG. 45—Transverse section of a tendon, showing the grouping of the tendon-tissue into primary, secondary, and tertiary bundles. × 80.

Dense fibrous tissue owes its characteristics to the more compact and orderly arrangement of the bundles of white fibres. Although the individual fibres are no thicker than in the areolar tissue, they are grouped into larger bundles and held more closely together by the inter-fibrillar cement or ground-substance. The bundles are disposed with greater regularity, either as closely packed parallel fasciculi, as in ligaments, tendon, and aponeuroses; or as intimately felted bands forming fibrous sheets, as in fasciæ, the cornea, and the dura mater. In the dense connective tissue the ground-substance often contains a system of definite interfascicular tissue-spaces, which, in suitably stained preparations, appear as irregularly stellate clefts (Fig. 34) that form, by union of their ramifications, a network of channels for the conveyance of the tissue-fluids throughout the dense structure. Where definite, as in the cornea or central tendon of the diaphragm, these spaces are almost, if not completely, filled by the stellate connective tissue cells which they enclose.

Tendon, the densest form of fibrous tissue, consists essentially of parallel bundles of white fibres. The individual fibres, held together by cement-substance, are assembled as **primary bundles.** A primary bundle, as seen in a cross-section of tendon, is represented by the area bounded by three or four

contiguous cells. In longitudinal section of tendon, it is seen as a linear band of fibres between two adjacent rows of cells. The primary bundles are grouped into **secondary bundles.** The latter are invested by a delicate sheath of areolar tissue. The secondary bundles are grouped into **tertiary bundles** by thicker partitions, or septa, of areolar tissue which are extensions of the general connective tissue envelope that surrounds the entire tendon. The larger septa surrounding the tertiary bundles support the blood-vessels and nerves and afford a path by which these gain the interior of the tendon. The blood-vessels, however, never penetrate the individual bundles, but are confined to the areolar tissue which invests them. The relations of the nerves to the tendon-tissue are described with the

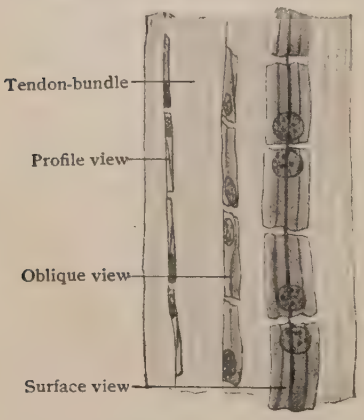


FIG. 46—Tendon-bundles from tail of mouse, showing different views of the tendon cells. × 300.

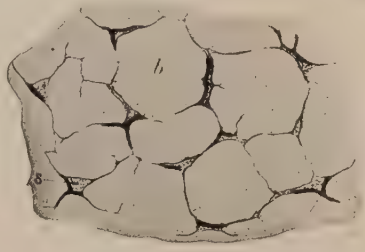


FIG. 47—Transverse section of primary tendon-bundles (*b*); the interfascicular spaces (*s*) contain the tendon-cells which surround the primary bundles. × 300.

Nerve-Endings. The primary bundles consist exclusively of white fibres and the cement-substance which contain collagen and tendo-mucoid, respectively. The **tendon-cells** occur in rows within the clefts between the primary bundles. Since each cell is in close contact with two or three bundles, the cytoplasm is moulded by the bundles into wing-like expansions. Seen from the surface, the tendon-cells appear as small rectangular elements, whose round nuclei are disposed in pairs, the nucleus of one cell lying close to that of its neighbor. Viewed in longitudinal profile, the tendon-cells appear as narrow rods, while when seen in transverse section, they are seen as stellate figures, the extended limbs of which are the sections of the wing-plates.

ADIPOSE TISSUE

The fatty material contained within the body is enclosed, to a large extent, within connective tissue cells in various localities. These modified elements are known as **fat cells,** which, together with the areolar tissue connecting the cells and supporting the blood-vessels, constitute adipose tissue.

The distribution of adipose tissue includes almost all parts of the body. Among the localities in which the accumulations of fat are conspicuous, are the subcutaneous areolar tissue, the orbits, the marrow of bones, the mesentery and the omentum, the subperitoneal tissue and the subpericardial tissue of the heart, the areolar tissue surrounding the kidneys, and the vicinity of

the joints. On the other hand, in a few situations, including the subcutaneous areolar tissue of the eyelids, the penis, the clitoris and labia minora, the lungs, except near their roots, and the interior of the cranium, adipose tissue is absent, even when developed to excess in other parts. As ordinarily seen, adipose tissue is of a light straw color and often exhibits a granular texture, due to the groups of fat cells within the supporting areolar tissue.

Examined microscopically in preparations from localities where they are not crowded and retain their individual form, the fat cells appear as large, clear, spherical sacs held together by delicate areolar tissue. Unless treated with some stain possessing an especial affinity for fat, as osmic acid or Sudan III, the oily content of the cells appears transparent and uncol-

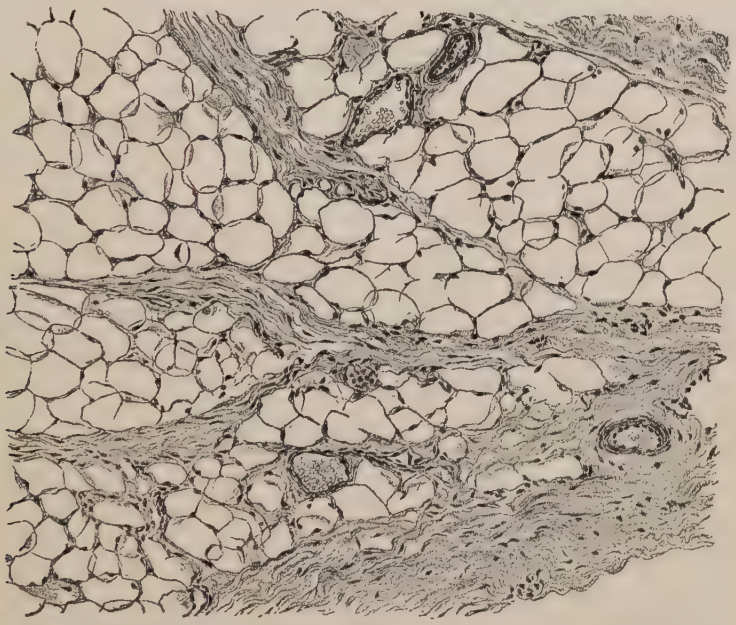


FIG. 48—Adipose tissue from omentum. The fat cells are arranged as groups between the bundles of connective tissue. × 160.

ored and seemingly occupies the entire cell-body. Critical examination, however, demonstrates the presence of an extremely thin peripheral layer of cytoplasm, which completely surrounds the huge oil-drops and at one place presents a local accumulation enclosing the displaced and compressed nucleus. In thin section of adipose tissue, by no means every fat cell exhibits a nucleus, since, owing to the small size of the latter in comparison with the diameter of the cell, many sections include zones lying beyond the nucleus. During life, the fat within the body is fluid. Quite often radiating clusters of slender **fat crystals** are observed within the adipose cells. These are margarin crystals that formed when the fat solidified after death.

Fat cells occur usually in groups supported and held together by highly vascular connective tissue. In localities possessing considerable masses of fat, as beneath the scalp and the skin, the cells are grouped into lobules

which appear as yellow granules to the unaided eye; in such positions the individual fat cells lose their spherical shape and assume a polyhedral form as the result of the mutual pressure of the closely packed vesicles.

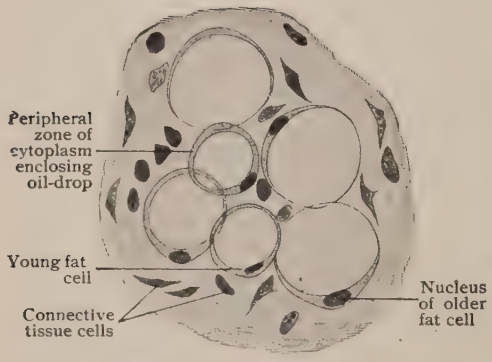


FIG. 49—Young fat cells from subcutaneous tissue. × 500.

In connective tissue elements about to become fat cells, minute isolated oil-drops first appear within the cytoplasm in the vicinity of the nucleus. These droplets increase in size and number, coalesce and gradually encroach upon the cytoplasm until the latter is reduced to a thin, almost inappreciable envelope, which completely invests the now huge distending oil-drops. The nucleus, likewise, is displaced towards the periphery, where it appears in profile as an inconspicuous crescent embedded within the cytoplasm (Fig. 49). When the invasion of the cell is extensive, the nucleus may contain minute oil-globules. Although many connective tissue elements, become transformed into fat cells at later periods, the earliest adipose tissue in some localities, as beneath the skin and in the orbit and omentum, is developed from highly vascularized lobular groups of mesenchymal cells (the **fat organs** of Toldt) which seem to be set apart for the production of such tissue. During prolonged fasting and extreme emaciation the fat cells may lose the greater part, or even their entire quota, of oily contents, which is then often replaced by a thin viscid cytoplasm that distinguishes the so-called **serous fat cells.** In other cases, after the disappearance of the oil-drops the fat cells return to a condition closely resembling that of the ordinary connective tissue cell.

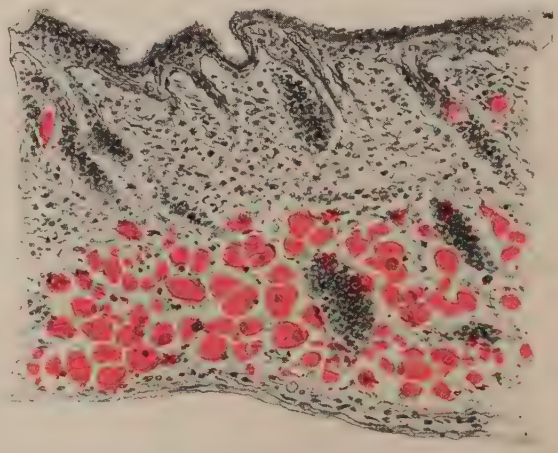


FIG. 50—Developing skin, with fat cells and beginning sebaceous secretion. Stained with Sudan III. × 144.

CARTILAGE

Cartilage includes a group of supporting tissues in which the intercellular substance undergoes increasing condensation until, as the hyaline variety, the intercellular matrix appears homogeneous, the constituent fibres

being so compact and closely blended that the fibrous structure is ordinarily no longer appreciable.

Depending upon the differences exhibited by the intercellular matrix, three varieties of cartilage are recognized, **hyaline**, **elastic**, and **fibrous.**

Hyaline cartilage, or gristle, is widely distributed, forming the articular surfaces of the bones, the costal cartilages, the larger cartilages of the larynx, the cartilaginous plates of the trachea and bronchi, the larger cartilages of the nose, and the middle part of the Eustachian tube. In the embryo the entire skeleton, with the exception of part of the skull, is mapped out by embryonal hyaline cartilage.

The intercellular **matrix** is apparently homogeneous, but after appro-

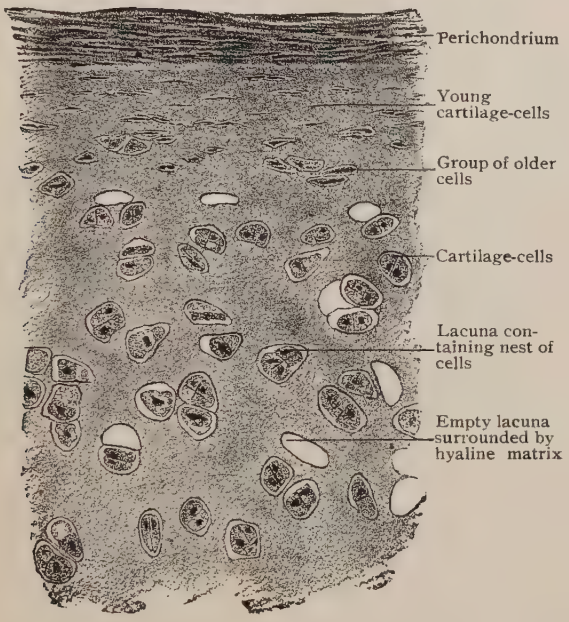


FIG. 51.—Transverse section of peripheral portion of costal cartilage showing hyaline cartilage. × 250.

priate treatment it is resolvable into bundles of collagenous fibres; ordinarily, however, these are so closely united and blended by the cementing ground-substance that the presence of the component fibres is not evident.

The **cartilage-cells,** as the connective tissue elements within the matrix are called, are irregularly oval or spherical nucleated bodies. They are lodged within the interfascicular spaces, or **lacunæ**, which they almost or entirely fill. In adult tissue usually two or more cells share the same compartment, the group being the descendants of the original occupant of the space. The matrix immediately surrounding the lacunæ is specialized as a layer of different density, which is described as a **capsule**; a further differentiation of the intercellular substance in the interior of adult cartilages is often seen. This consists of a deeper staining of the matrix around groups of lacunæ lying close together, thereby producing the local territories known as the

cell-areas. The lacunæ of hyaline cartilage are homologous with the tissue-spaces of other dense connective tissues, although channels establishing communication between the adjacent lacunæ are not demonstrable in the higher vertebrates.

The free surface of cartilage is covered by an envelope of dense connective tissue, the **perichondrium.** The latter consists of a compact external **fibrous layer** and a looser inner or **chondrogenetic layer,** containing many connective tissue cells. The latter are disposed in rows parallel to the surface of the cartilage, and during the peripheral growth of the tissue, gradually assume the characteristics of cartilage cells, being at first spindle-shaped and later ovoid and spherical. The young cartilage cells thus formed become gradually separated by increasing tracts of the newly deposited intercellular matrix. As the groups of cells arising from the division of the transformed elements recede from the perichondrial surface, they lose their parallel disposition and become irregularly arranged and further separated. In addition to the **perichondrial growth** at the surface, cartilage also increases by **interstitial growth** effected by the formation of new cells and the associated matrix in the interior of the cartilage. The interstitial method is identified with the expansion of the embryonal cartilages, while the perichondrial one is conspicuous in bringing about the additions of new cartilage during the later growth of cartilages.

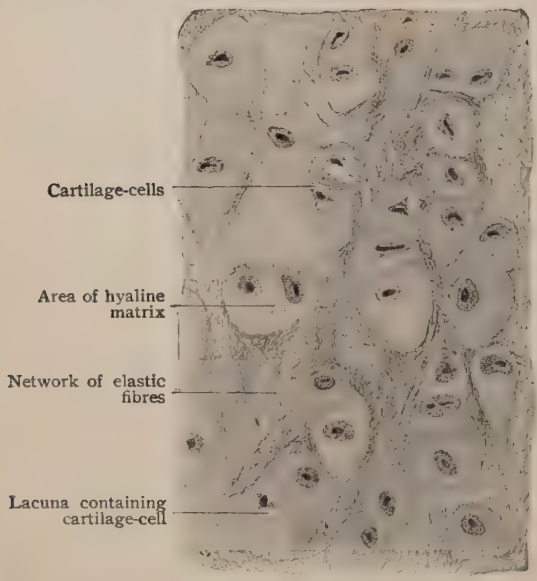


FIG. 52—Section of elastic cartilage from the epiglottis. × 360.

In articular cartilage the superficial zone contains sparsely distributed groups of small cells arranged parallel to the free surface. Within the deeper strata, these groups are replaced by elongated rows of larger elements lying perpendicular to the articular surface. This columnar disposition of the cartilage-cells is particularly evident towards the underlying epiphyseal bone.

In parts of the cartilage remote from the perichondrium, the matrix sometimes exhibits **areas of calcification** due to deposits of lime-salts. These are common in certain tissues, as the costal cartilages of aged subjects, although similar changes are almost always present in the laryngeal cartilages, particularly the thyroid and the cricoid, as early as the twentieth year. They may progress until complete calcification of the cartilage occurs. Histologically this alteration consists of a deposit of the inorganic material

within the matrix and is not true osseous tissue, as implied by the frequently misapplied term "ossification."

The **blood-vessels** of cartilage are usually limited to the periphery, within the perichondrium or the associated synovial membranes. Nutrition of the cartilage is maintained by imbibition of the tissue-fluids through the matrix into the lacunæ. In the thicker masses, as in the cartilages of the ribs, nutrient canals exist in those portions most remote from the perichondrium. Such spaces contain a small amount of areolar tissue supporting the blood-vessels; the latter, however, are limited to the canals and the nutrition of the cartilage-tissue is effected here, as elsewhere, by absorption through the matrix. The **lymphatics** are sparingly present in the perichondrium. **Nerves** never have been demonstrated within the cartilages, which fact is in accord with the insensibility of these tissues and their adaptation to the friction, concussion, and compressions incident to their functions.

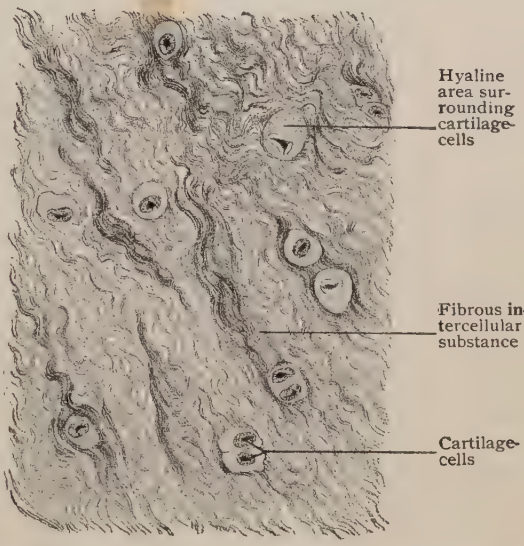


FIG. 53—Section of fibrous cartilage from intervertebral disk. × 225.

Elastic cartilage, called also *yellow elastic* and *reticular* cartilage, has a limited distribution, occurring principally in the cartilages of the external ear, lower part of the Eustachian tube, and in parts of the larynx, namely, the epiglottis, the cuneiform and corniculate cartilages, and the vocal processes and apices of the arytenoids. In its physical properties this variety differs from hyaline cartilage, as it is dull yellowish in color and pliable and tough in consistence, in contrast to the bluish opalescent tint and comparative brittleness of hyaline cartilage.

The characteristic histological feature of elastic cartilage is the presence of elastic fibres within the intercellular matrix. The lacunæ containing the cartilage-cells are immediately surrounded by limited areas of hyaline matrix, the so-called "capsules" of some authors. The matrix between these homogeneous areas, however, is penetrated by delicate and often intricate networks of elastic fibres. The latter respond, as in other localities, to specific stains. The method by which the elastic fibres develop is uncertain, although their production must be attributed to the influence of the cells. Since the fibres appear relatively late and within the matrix often at some distance from the cartilage-cells, it is probable that they do not arise within the exoplasm of the cells. The elastic cartilages are surrounded by a perichondrium of the usual description.

Fibrous cartilage, or *fibrocartilage,* is found in comparatively few localities, although it occurs in masses of considerable bulk. Its chief situations are the intervertebral disks, the symphyses, the marginal plates and interarticular disks of certain joints, the sesamoid cartilages, and the lining of bony grooves for tendons. In its physical properties, this tissue combines the flexibility and toughness of fibrous tissue with the firmness and elasticity of cartilage. In structure, fibrous cartilage resembles dense fibrous connec-

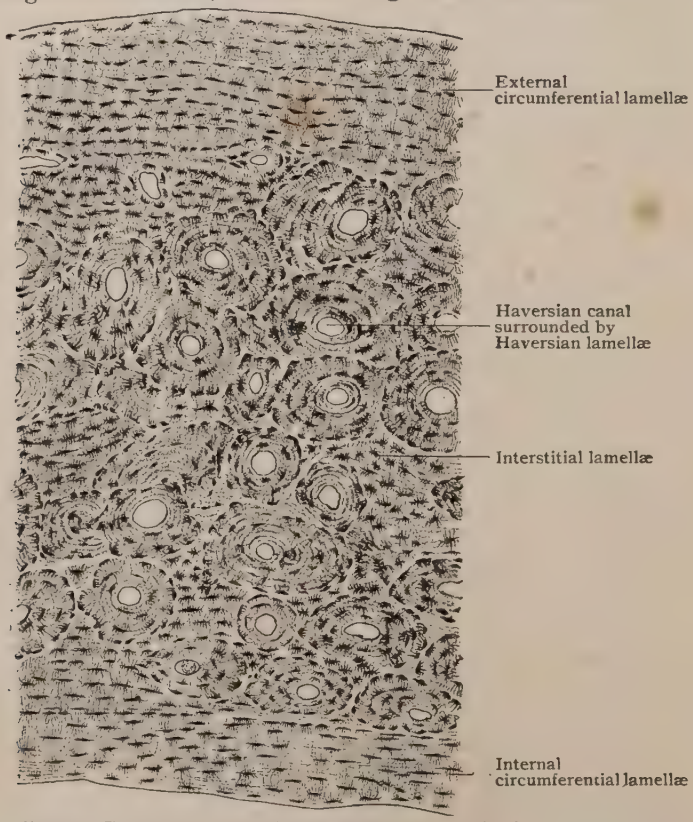


FIG. 54—Transverse section of compact bone; the section has been ground and dried, hence the lacunæ are filled with air. × 70.

tive tissue, since the principal constituents of its matrix are the wavy bundles of closely packed white fibres. Between these bundles lie small irregularly distributed oval areas of hyaline matrix, which immediately surround the cartilage-cells, singly or in groups. The number of cells and the proportion of fibrous matrix differ in various localities. A distinct perichondrium is wanting.

BONE

Bone, or osseous, tissue is a dense form of connective tissue, the matrix of which is impregnated with calcium salts; to this modification, shared by the dentine of the teeth, is due the characteristic hardness of the tissue.

Bone consists of two parts, an organic and an inorganic portion, the former giving toughness and the latter hardness to the osseous tissue. The organic part of bone may be removed by calcination, the inorganic constituents remaining undisturbed. After such treatment, while retaining its form, the bone is fragile and easily crushed and has suffered a loss of one-third of its weight, due to the destruction and elimination of the organic matter. The inorganic material, on the other hand, may be removed by the action of dilute hydrochloric acid leaving the organic part intact. Treated in this manner, the bone, although retaining perfectly its details of form, is tough

FIG. 55—Section of frontal bone, showing the spongy bone enclosed within the lamellated compact bone; the latter, however, does not contain Haversian systems. × 18.

and flexible, a decalcified rib or fibula being readily tied into a knot. The organic constituents, consisting chiefly of **collagen** and **osseo-mucoid,** yield **gelatin** after boiling with water. The inorganic constituents which form approximately two-thirds of the bone, include a large percentage of calcium phosphate, much less calcium carbonate, with small proportions of calcium fluoride and chloride, and of the salts of magnesium and sodium. In oven-dried compact bone, the organic content averages 37.15 per cent. of the total dried weight within the ages of twenty to sixty years, and 36.22 per cent. between sixty-one and ninety years (Radasch, '21).

On sawing through a bone from which the marrow and other soft parts have been removed, the osseous tissue is seen to be arranged as a peripheral zone of **compact bone** enclosing a variable amount of **cancellated,** or **spongy,**

bone. In the typical long bones, as the humerus and femur, the compact tissue almost exclusively forms the tubular shaft enclosing the large **marrow-cavity,** while the cancellated tissue constitutes the expanded extremities with the exception of a narrow superficial stratum of compact bone. The irregular clefts between the lamellæ of the spongy bone are direct extensions of the general medullary cavity and are filled with marrow-tissue. In the flat bones of the skull, the compact substance is arranged as an outer and an inner plate, or **tables,** of considerable thickness, between which lies the spongy bone, or **diploë.** The short and irregular bones are made up of an inner mass of spongy bone covered everywhere by a shell of compact substance, which often is locally thickened to insure additional strength where needed.

The **cancellated** or **spongy bone** consists of delicate trabeculæ and lamellæ united into an intricate osseous reticulum well calculated to yield strength without undue weight. In many positions, conspicuously in the neck of the femur, the more robust lamellæ are disposed according to a definite plan in order to meet the strains of pressure and of tension. Although composed of the same structural elements, compact and spongy bone differ in their histological details in consequence of the secondary modifications which take place during the conversion of the spongy bone, the original form, into the compact. To obtain the classic picture of bone-tissue, in order to study its general arrangement where most typical, it is desirable to examine thin ground sections of the compact substance cut at right angles to the axis of a long bone which has been macerated and dried.

The **compact bone** in such preparations, when examined under low magnification (Fig. 54), is seen to consist of osseous layers arranged as three chief groups: (**a**) **circumferential lamellæ,** which extend parallel to the external and internal surfaces of the compact bone (**b**) **Haversian lamellæ,** which are disposed concentrically and form conspicuous annular groups, the Haversian systems, enclosing the Haversian canals; and (**c**) **ground,** or **interstitial lamellæ,** which include the irregularly arranged tracts filling the intervals between the Haversian systems and the surface lamellæ.

Each **Haversian system** consists of the concentrically disposed lamellæ and the centrally situated channel, the **Haversian canal,** which encloses prolongations of the marrow-tissue and ramifications of the medullary blood-vessels. Between the annular lamellæ are seen small spindle-shaped or oval spaces, the **lacunæ,** (about 20 μ long, 10 μ wide, and 6 μ thick) from which minute passages, the **canaliculi,** radiate and join with others to establish communication between the adjacent lacunæ of the same Haversian system. The lacunæ and canaliculi thus form an intercommunicating network of tissue-spaces similar to those in other dense connective tissue. When viewed in profile, as they are in sections cutting the lamellæ at right angles, the lacunæ present their smaller dimensions and appear as minute fusiform spaces; seen in sections which pass parallel to the lamellæ (Fig. 56), the

lacunæ are broader and more circular, the spaces with the canaliculi forming the spider-like figures so conspicuous in sections of dried bone.

The characteristic disposition of the lamellæ of the Haversian system is due to the secondary formation of the bone-tissue during the conversion of the spongy bone into the compact, the circumference of each system corresponding to an **Haversian space.** As a preliminary step in the conversion of spongy into compact bone, the spaces within the spongy bone usually are enlarged through the activity of osteoclasts. These enlarged spaces of the spongy bone are the Haversian spaces. Within the walls of the Haversian

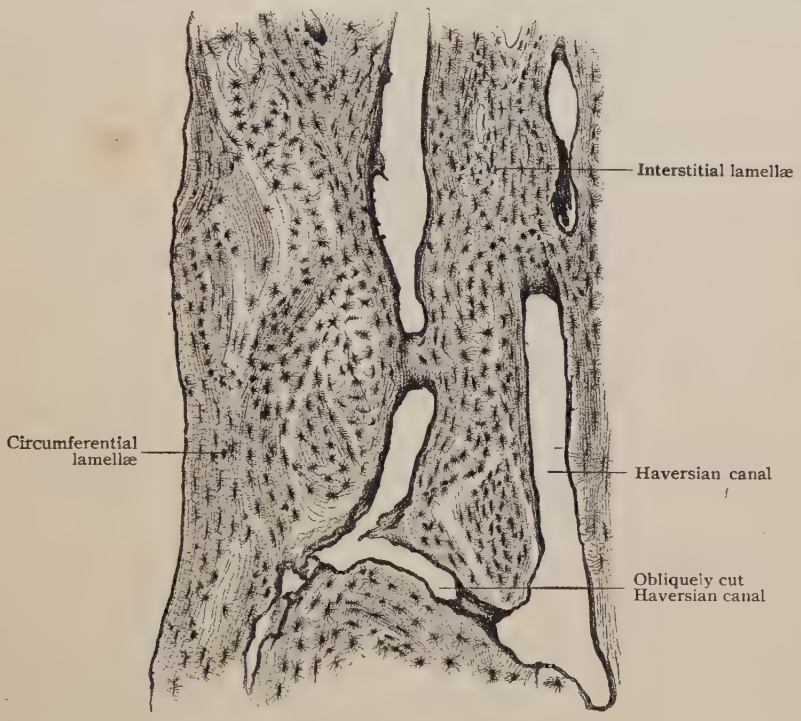


FIG. 56—Longitudinal section of compact bone, ground and dried. × 70.

spaces there are laid down successive layers of bone, the *concentric* or **Haversian lamellæ.** The narrow tubular channel remaining within the concentric lamellæ is an Haversian canal. The lamellæ constituting the original framework of spongy bone, and now seen between the Haversian systems are called the **interstitial lamellæ.** Thus it is seen that the Haversian systems exist only in compact bone. When deprived of the mineral matters and examined in thin fragments, the osseous lamellæ, often exhibit indications of the fibrous structure which they really possess, since the bone-matrix consists of closely felted bundles of white fibres united by cement-substance. On examining decalcified bone, either in section or after being pulled apart, bundles of fibrous tissue are seen which penetrate the outer circumferential lamellæ in a direction perpendicular or oblique to the surface and thus pin

or bolt the layers together. Such bundles, the **perforating fibres of Sharpey,** are numerous in the lamellæ beneath the periosteum, from the inner layer of which membrane they are derived. The perforating fibres consist of bundles of fibrous tissue, with a variable number of elastic fibres; since they are often imperfectly calcified, on drying they leave minute canals which pierce the lamellæ from the surface of the bone. Being produced by the periosteum, Sharpey's fibres are never found in the secondary lamellæ constituting the Haversian systems.

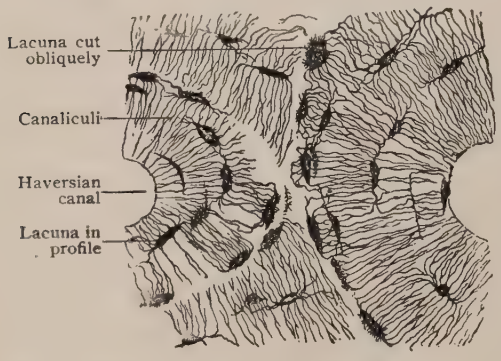


FIG. 57—Portion of adjacent Haversian system cut transversely. × 250.

The **Haversian canals** (.05—.1 mm. in diameter) are continuations of the medullary cavity and in the case of the larger ones, contain prolongations of the marrow-tissue. They serve the important purpose of carrying blood-vessels into the interior of the compact bone. From these vessels the nutritive fluids pass into the canaliculi and the lacunæ and so on through the dense tissue, the nutrition of the lamellæ and the enclosed bone-cells being in this manner insured. The individual canals are short and communicate by oblique branches with adjacent channels. They also indirectly communicate with the external surface of the bone by means of passages, the **Volkmann canals,** within the circumferential lamellæ. These canals open on the surface and convey twigs from the periosteal blood-vessels, primarily into the lamellæ other than those of the Haversian systems. The twigs entering by the superficial canals freely anastomose with those within the Haversian canals, the compact bone being thus provided with a vascular network derived from both sources.

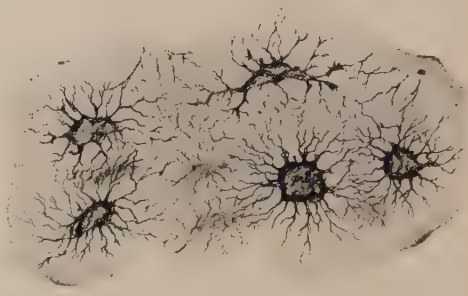


FIG. 58—Lacunæ and canaliculi in dried bone, cut parallel with the lamellæ. × 300.

The **bone-cells** are connective tissue elements imprisoned within the lacunæ, an arrangement similar in principle to that within the cornea where the corneal cells lie within the tissue-spaces of the ground-substance. Ground sections of dried bone afford the best pictures of general arrangement of the intercellular matrix, but are inadequate for the study of the bone-cells, since the latter are shrunken and lost in the *debris* which, with air, fills the lacunæ in the ground specimens. In order to exhibit the bone-cells, after fixation the tissue is decalcified, embedded, sectioned, stained, and mounted in

the usual manner. By such treatment the preservation of the cells is insured although the lacunæ and canaliculi no longer show with diagrammatic sharpness in consequence of being permeated with the mounting medium instead of air. The bone-cells, after being stained in such decalcified sections, appear as small lenticular or stellate bodies within the lacunæ, which they almost or entirely fill (Fig. 59). The peripheral portions of their cytoplasm extends from the stellate cell-body into the canaliculi as delicate processes of variable length.

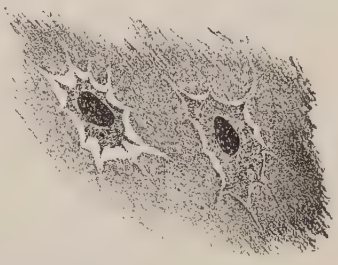


FIG. 59—Bone-cells lying within the lacunæ. × 530.

The Periosteum.—The external surface of bones is closely invested, except when covered with cartilage by a fibrous membrane, the **periosteum,** a structure of great importance during development and growth, and later, for the nutrition and repair of the osseous tissues. The adult periosteum consists of two layers, an outer dense **fibrous** and an inner **fibro-elastic;** during periods of

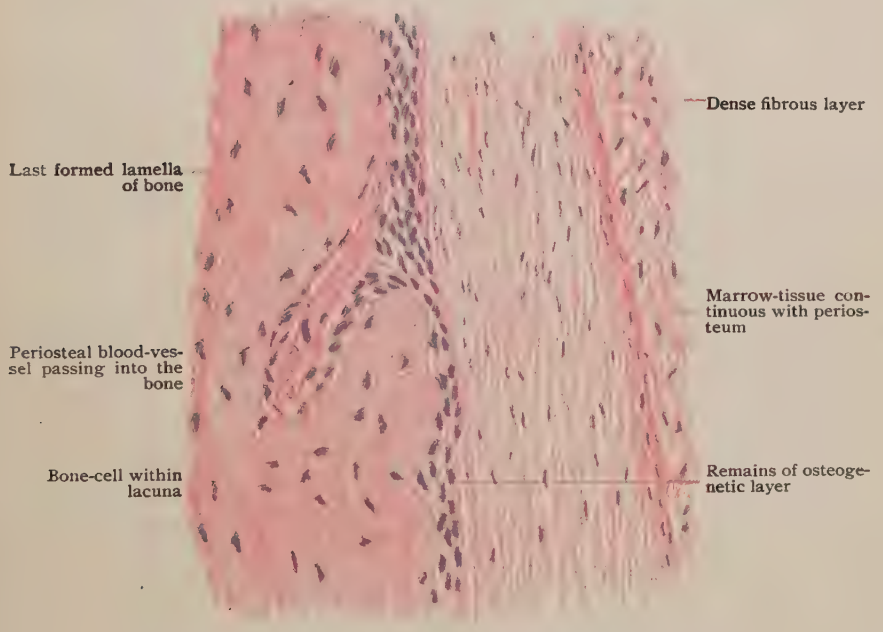

Dense fibrous layer
Last formed lamella of bone
Marrow-tissue continuous with periosteum
Periosteal blood-vessel passing into the bone
Bone-cell within lacuna
Remains of osteogenetic layer

FIG. 60—Section of young periosteum and subjacent bone. × 275.

growth, an additional stratum, the **osteogenetic layer,** lies within the latter in close relation with the exterior of the bone.

The **fibrous layer** is composed of bundles of fibrous tissue and supports the larger blood-vessels which, within the deeper parts of the periosteum, break up into twigs that enter the surface of the bone through the

Volkmann canals. The **fibro-elastic layer** includes a feltwork of elastic fibres and of more delicate strands of fibrous tissue. The inner surface of the periosteum is attached to the underlying bone by processes of connective tissue which accompany the blood-vessels into the superficial canals. This relation persists from the continuity of the formative tissue of the young periosteum with the early marrow-tissue.

The **osteogenetic layer,** during development and growth of the bone, consists of delicate bundles of fibrous tissue and large numbers of round or fusiform connective tissue cells of an embryonal type. Those next the growing bone are of irregular cuboid form and disposed in a single row upon the surface of the developing osseous tissue. Since these cells are directly concerned in producing the new bone, they are termed **osteoblasts.** As they become surrounded by the products of their own activity, they become imprisoned within the bone-matrix and are then called bone-cells. After completion of its active rôle, the osteogenetic layer becomes greatly reduced and inconspicuous, in the adult periosteum being represented by flattened cells, which no longer form a continuous stratum but occur as scattered groups.

In addition to its important bone-producing function, the periosteum serves as the immediate means by which muscles, tendons, ligaments, and fasciæ gain attachment to the skeleton. In every case the union is effected by the fusion and blending of the connective tissue of the attached structure with the outer layer of the periosteum.

Bone-Marrow.—The spaces in the interior of bones, whether the large medullary cavities surrounded by the compact substance forming the tubular shaft of the long bones or the irregular interstices between the trabeculæ of the cancellated tissue, are filled with bone-marrow. The latter also extends into the larger Haversian canals. Apart from its fundamental relations to the development of bone, in addition to supporting the medullary blood-vessels and therefore assisting in maintaining the nutrition of the bone, the marrow plays a very important rôle in connection with the production of blood-cells. Indeed, with its chief functions in mind, bone-marrow is classed as a **blood-forming organ,** and, as such, finds its systematic consideration with the blood.

Although of a reddish tint within all the bones of the early skeleton, the marrow in the adult includes two kinds—the **red** and the **yellow.** Thus, within the shaft of the long bones it appears as a light yellowish tissue, presenting the characteristics of ordinary adipose tissue; while within the upper ends of the humerus and of the femur, and especially within the bodies of the vertebræ, the ribs, the sternum, and the diploë of the cranium, the marrow possesses a dull red color.

Red Marrow.—The ingrowth of the periosteal tissue and blood-vessels constitutes the primary marrow of the fetal skeleton; from this tissue the red marrow filling the young bones is directly derived. The red marrow is, therefore, the first formed and typical variety. After early childhood, however, the marrow within the bones of the extremities suffers gradual invasion by fat, until, with the exception of the marrow within the upper ends of the

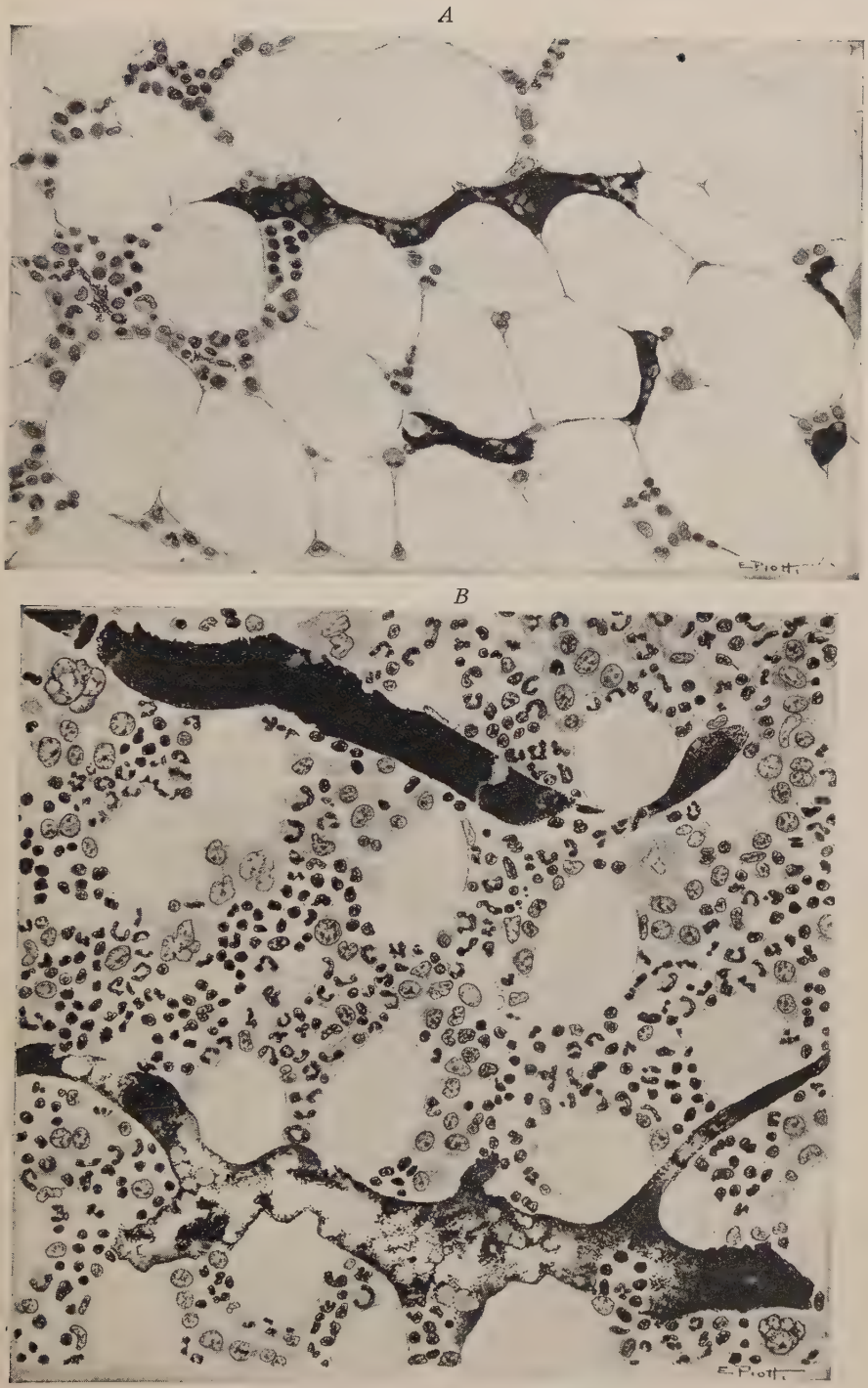


FIG. 61—Camera lucida drawings, × 500: *A*, of the vessels in a relatively non-cellular region of the femoral marrow from rabbit; *B*, of a comparatively cellular marrow taken from a normal rabbit. (*From Drinker, Drinker, & Lund, '22*).

humerus and the femur, the red tissue gives way to the yellow, the fat cells replacing most of the original marrow-elements.

When examined in section after fixation and appropriate staining, the adult red marrow exhibits a delicate connective tissue reticulum which supports the blood-vessels and contains within its meshes numerous cells (Fig. 61). **Fat cells** are practically always present, and show as clear spaces lined by a thin, but distinct membrane. The **reticulum cells** are large palely-staining cells, with rounded vesicular nuclei. They are more plainly seen where the blood-formative cells are few. Of the blood-vessels, those most characteristic of the bone-marrow are the numerous, thin-walled venous sinusoids, lined by **endothelium.** Next the bone, the fibrous tissue forms a thin membrane, the **endosteum,** lining the medullary cavity and extending into the larger Haversian canals. The more characteristic cells connected with blood-formation include (1) the **megakaryocytes,** or giant cells; (2) the immature forms of granular leucocytes (**myelocytes,** or **granuloblasts**); and (3) the immature forms of erythrocytes (**erythroblasts**). In addition there are (4) **hemoblasts,** or **hemocytoblasts,** the earliest form of the blood-formative cells, and also (5) mature granular leucocytes and erythrocytes.

The **megakaryocytes,** the mononuclear giant cells of the marrow, are huge and conspicuous occupants of the reticular meshes. They must not be confused, however, with giant cells of another kind, the *osteoclasts*, which are present in the young marrow of developing bones. The distinguishing feature between the two is the nucleus, which in the case of the osteoclast is multiple and in that of the megakaryocyte usually single. In the last instance, however, the nucleus may assume a very complex contour, sometimes being so lobulated and contorted that what is really one continuous nucleus appears as several. The osteoclasts are always multinuclear, two or more ovoid nuclei occupying the huge mass of granular cytoplasm. These cells, moreover, lie close to the trabeculæ of young bone, a position in keeping with their particular function as bone-destroyers. The megakaryocytes are regarded as producers of the blood-platelets (J. H. Wright, '10).

Myelocytes, or *granuloblasts*, often constitute the majority of the cells seen in the red marrow. They give rise to the granular leucocytes, which have specific granules in their cytoplasm and have nuclei of irregular forms. The myelocytes are cells with single round nuclei, but already possess the specific granules. These are named, according to their staining affinities, neutrophilic, acidophilic, or basophilic. The acidophilic, or eosinophilic, granules are the ones most readily seen because of their size and distinctive color of staining.

The **erythroblasts** are nucleated cells which by the loss of their nuclei, will give rise to the erythrocytes of the circulating blood. In their earliest stage the erythroblasts are not easily distinguished, but when they begin to contain hemoglobin they have a distinctive color and staining reaction in the cytoplasm. At the same time there is a decrease in size of the nucleus, the chromatin becoming closely massed together to form a small dark-staining nucleus. These nuclei are the smallest seen in bone-marrow cells.

The **hemocytoblasts,** or *hemoblasts*, are the earliest progenitors of the

blood-cells, and appear in adult bone-marrow in comparatively small numbers. In order to be sure of their identification the tissues must be preserved and stained by special methods. The cells are usually but not always large. The nucleus is round and occupies the greater part of the cell. The chromatin is in the form of fine particles evenly distributed through the nucleus. Several nucleoli are usually present. The cytoplasm stains deeply blue and there are no granules of any kind. The identification of this type of cell in sections, by Maximow's technic of azur-eosin staining after parlodion-embedding, has greatly advanced the study of the blood-formative tissues.

There are also present a certain number of **mature granular leucocytes** and **erythrocytes.** The granulocytes are characterized by their irregular shapes of nuclei and by their specifically-staining cytoplasmic granules. The erythrocytes have lost their nuclei, and the hemoglobin is present throughout the cytoplasm. A more complete description of the above forms, as well as of other cells found in marrow will be given under Development of Blood-Cells.

Yellow Marrow.—After early childhood, the red marrow, which previously fills all the medullary spaces, begins to suffer invasion by fat cells and conversion into adipose tissue. This change, which results from the substitution of fat cells for the distinctive marrow components, affects the medullary tissue within the long bones of the extremities, except within the upper ends of the humerus and femur. Examined in section, the yellow marrow resembles ordinary adipose tissue, consisting chiefly of the large fat cells supported by a reticulum of connective tissue. The cells belonging to the latter, together with small residual groups of blood-formative cells, are the usual elements encountered. In advanced age and during starvation, the customary consistence and yellow color give place to a mucoid condition and reddish tint, the fat cells of such **gelatinous marrow,** as it is termed, losing much of their oily contents.

Blood-Vessels of Bones.—The generous blood-supply of bones is arranged as two sets, the **periosteal** and the **medullary.** The former constitutes a network within the periosteum and supplies twigs which enter the subjacent compact bone through the Volkmann canals and communicate with the branches from the medullary system. The medullary artery is often, as in the case of the long bones, a vessel of considerable size, which, accompanied by the companion veins, traverses the oblique nutrient canal to gain the centre of the marrow. On reaching this position the medullary artery usually divides into ascending and descending branches, from which twigs radiate towards the periphery of the marrow cavity. The twigs terminate in arterial capillaries, which expand rather abruptly into larger venous sinusoids, in consequence of this arrangement the rapidity of the blood-stream becoming diminished in its course through the marrow. The endothelium forms a continuous lining throughout these vessels (Drinker, '22; Doan, '22). After thus coming into close relations with the marrow-tissue, the blood is collected into veins destitute of valves. Many of these veins enter the central longitudinal vein, while others pass towards the periphery

of the marrow. In addition to the companion veins which accompany the medullary artery through the nutrient canal, in many instances the larger veins pursue an independent course and emerge from the cancellous tissue by means of special canals piercing the compact substance.

Definite **lymphatics** are found within the periosteum, and probably exist also in the marrow, inasmuch as foreign material injected into the marrow is seen to drain away through lymphatics.

The **nerves** supplying the bones include both myelinated and unmyelinated fibres. The latter, distributed partly to the periosteum and partly within the bone, are chiefly sympathetic fibres destined for the control of the involuntary muscle within the walls of the blood-vessels. The myelinated sensory fibres run within the periosteum, some being connected with special endings of the lamellar type.

DEVELOPMENT OF BONE

All bone, wherever found, is formed through the activities of specialized connective tissue cells, the **osteoblasts.** Because the immediate surroundings of the sites of the osteoblastic activity present several well-defined and constant differences there are said to be several methods of bone-formation. In regard to the actual deposition of bone, however, the methods are all the same, since all depend on the capacity of the osteoblasts to form an intercellular substance, in which calcification takes place. The three methods of bone-formation are (1) **direct,** or **intramembranous,** (2) **endochondral,** (3) **periosteal** (including **perichondrial**). By the direct, or intramembranous, method of bone-formation develop the bones of the vault of the cranium, and of the greater part of the face. The bone-matrix is formed by the osteoblasts directly within the layer of young connective tissue, at the site of the future bone. The other two methods both take part in the formation of bones which are preceded by cartilage. By the endochondral method osseous tissue is produced within the cartilage, and by the perichondrial method bone is formed outside the cartilage. The perichondrial method becomes the periosteal method as soon as bone has been formed around the cartilage, so that the term perichondrial applies only to the earliest phase and the term periosteal to all later phases. On this account the whole series of stages, even from the beginning formation around the cartilage, is for convenience termed periosteal. Both endochondral and periosteal methods take part in the formation of the completed bone, although their contribution to the final results are not only unequal, but vary with different types of bones.

The greater part of the bone formed within cartilage undergoes absorption, the spongy substance within the ends of long bones and within the bodies of irregular bones representing the chief persisting contribution of endochondral, or intracartilaginous, bone. Even when the intracartilaginous changes are conspicuous, as in the development of the humerus, femur, and other long bones, the important compact substance of the mature bone is the product of the periosteal connective tissue. Although the

formative processes involved in both endochondral and periosteal bone formation proceed coincidently and are closely related, as a matter of convenience they will be described separately and as occurring in the development of a typical long bone.

Endochondral Bone-Development.—The primary cartilage, formed by the proliferation and condensation of the mesenchymal tissue, gradually assumes the characteristics of embryonal cartilage, which by the end of the second month of fetal life, maps out the principal segments of the skeleton.

The initial changes within the cartilage appear at points known as **centres of ossification.** These early changes involve both cells and matrix, which exhibit conspicuous increase in size and amount, respectively. The cartilage-cells become larger and more vesicular (Fig. 62) and encroach upon the intervening matrix, in which a deposit of lime salts now takes place, as shown by opacity and by the grittiness when a knife is carried through such centres. On acquiring their maximum size, the cartilage-cells soon give indications of impaired vitality in their shrinking cytoplasm and degenerating nuclei. The enlarged spaces or lacunæ enclosing these cells are known as the **primary areolæ.**

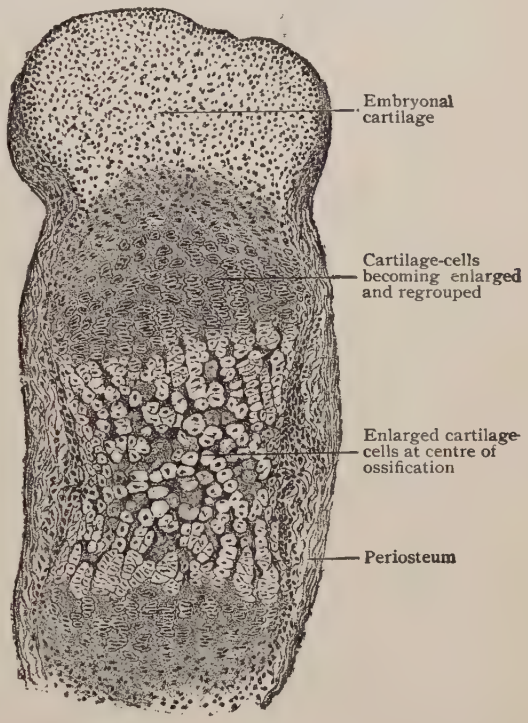


FIG. 62—Section of tarsal bone of fetal sheep, showing centre of ossification. × 50.

Coincidently with these changes within the cartilage, changes are seen in the perichondrium in the areas near the centres of ossification. Bud-like processes of the perichondrial layer grow inward and invade the embryonal cartilage, by absorption of the cartilage-matrix gaining the centre of ossification and there effecting destruction of the less resistant cells and the intervening matrix. There are believed to be special cells for this destruction of the cartilage, termed **chondroclasts.** In consequence of this invasion by the perichondrial tissue, a space, the **primary marrow-cavity** now occupies the centre of ossification and contains embryonic connective tissue having the same potentiality for bone-formation as that on the exterior of the cartilage. This tissue, the **primary marrow,** which has thus gained the interior of the cartilage, contributes the cells upon which a double rôle devolves—to remove the embryonal cartilage and to produce bone.

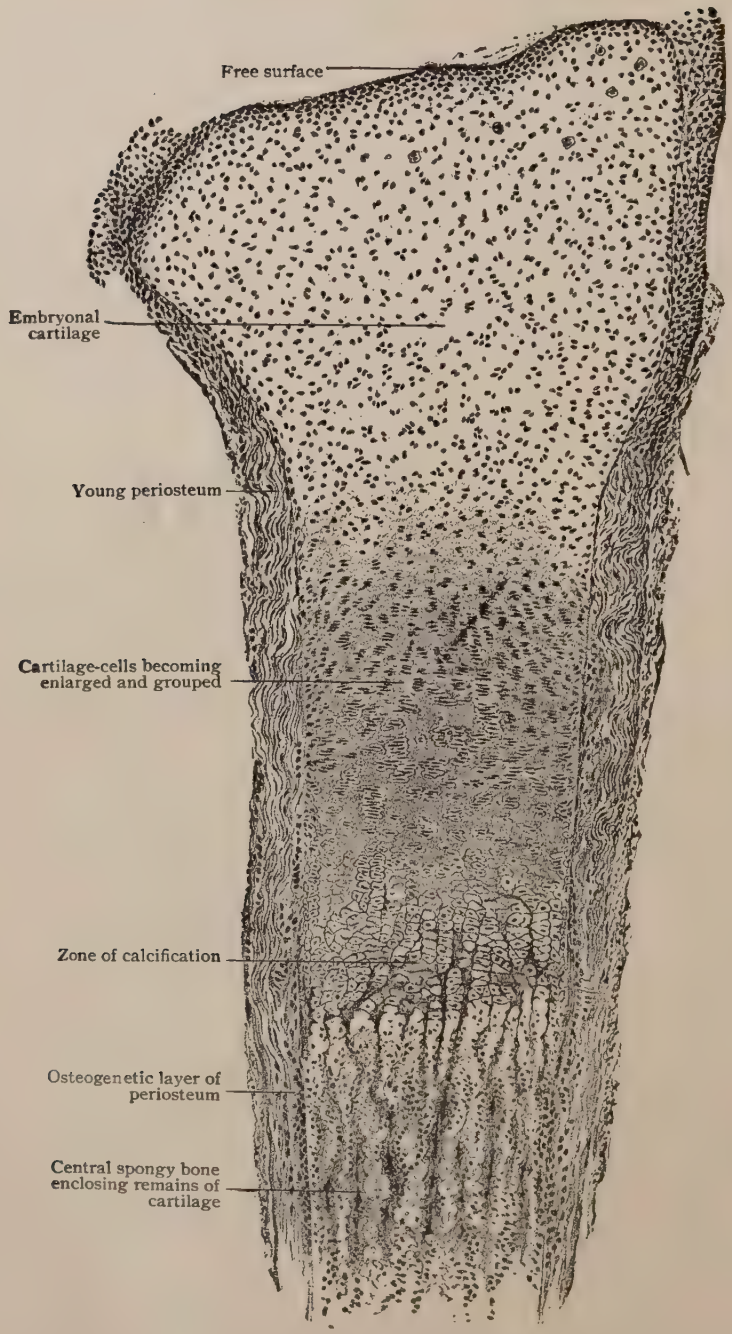


FIG. 63—Longitudinal section of metatarsal bone of fetal sheep, showing endochondral bone development. × 40.

The cartilage-matrix closing the enlarged cell-spaces on the side towards the primary marrow-cavity progressively suffers absorption whereby the spaces are opened, are converted into **secondary areolæ,** and are brought into direct communication with the expanding medullary cavity. The cartilage-cells are set free from their lacunæ into the marrow-cavity and undergo disintegration, taking no part in the direct production of the bone-tissue.

Beyond the immediate limits of the primary marrow-cavity, the cartilage-cells in their turn undergo the increase in size and the impairment of vitality described; in addition they often exhibit a conspicuous rearrangement, forming columnar groups separated by intervening tracts of calcified matrix (Fig. 63). This characteristic belt, the **zone of calcification,** surrounds the medullary cavity and marks the area in which the destruction of cartilage is progressing with greatest energy. In consequence of the disposition of the cartilage-elements as columnar groups separated by intervening tracts of calcified matrix, a less and a more resistant portion of the cartilage are offered to the attacks of the marrow-tissue by the cell- and the matrix-columns, respectively. As the result of this difference, the cells and the immediately surrounding partitions first succumb, while the intercolumnar tracts of calcified matrix remain for a time as irregular indented tapering processes, deeply tinted in sections stained with hematoxylin, and extending beyond the last row of cartilage-cells into the medullary cavity. These trabeculæ of calcified cartilage-matrix serve as supports for the marrow-cells engaged in producing the true bone. These specialized connective tissue elements, the **osteoblasts,** become arranged along the cartilaginous trabeculæ and through their influence the immature bone-tissue is deposited.

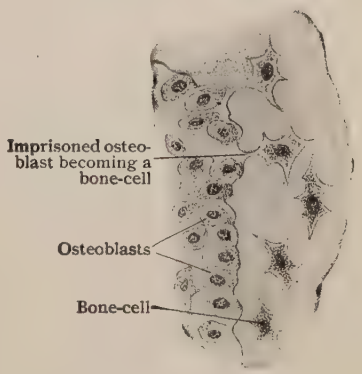


FIG. 64—Portion of developing osseous trabecula and osteoblasts. × 350.

Simultaneously with the **destructive** phase attending the absorption of the embryonal cartilage by the **chondroclasts,** the **constructive** process of bone-formation is instituted by the osteoblasts. The osteoblasts rest on the irregular trabeculæ of calcified cartilage and bring about the deposit of a layer of bone-matrix upon the surface of the trabeculæ, which thus becomes encased within a shell of immature bone. After the latter has attained a thickness at least equal to that of the osteoblasts, some of the latter are gradually surrounded by the osseous matrix, until, finally, they lie within the newly formed bone as its cells (Fig. 64). The **bone-cells** are, therefore, imprisoned osteoblasts, which, in turn, are specialized connective tissue elements. The bone-cells occupy minute lenticular or stellate spaces, the **primary lacunæ.** The bone-matrix is at first devoid of calcareous material and is, therefore, soft; very soon, however, the deposit of lime-salts begins and the young bone becomes hard. The increase of the new bone is attended by the gradual disappearance of the enclosed calcified cartilage-matrix, the

last traces of which, however, persist for some time as irregularly deeply stained patches within the osseous trabeculæ, at some distance from the zone of calcification (Fig. 63). Many of the newly formed bony trabeculæ also soon undergo absorption, with corresponding enlargement of the intervening marrow-spaces. The remaining trabeculæ increase in thickness by the addition of new lamellæ on the surface covered by the osteoblasts and form a trabecular network, the **primary central spongy bone.** In the adult irregular bones, the primary spongy bone is represented by the cancellated tissue forming the internal framework. In the adult long bones, the primary spongy bone undergoes further absorption within the middle of the shaft, simultaneously with its continued development within the cartilage at the ends of the diaphysis, or shaft. As the result of this absorption, a large space, the **central marrow-cavity,** is formed, the growth of which keeps pace with the general expansion of the bone. As long as a long bone increases in length, new cartilage is added at the ends of the shaft, to be replaced in its turn by the advancing osseous tissue.

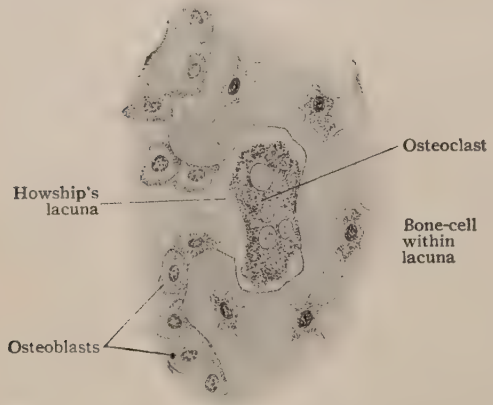


FIG. 65—Portion of trabecula of spongy bone undergoing absorption by osteoclast. × 450.

The **absorption** of the newly formed bone is effected through the agency of large polynucleated cells, the **osteoclasts.** These are specialized marrow-elements whose particular rôle is the breaking down and absorption of the bone-matrix. They are very large (50–100 μ) and lie, singly or in groups close to the surface of the bone within depressions, the so-called **Howship's lacunæ,** produced by the erosion of the osseous matrix (Fig. 65). In long bones, the only part of the central spongy bone which persists after their development and growth is completed, is that constituting the cancellated tissue within their ends. It will be seen, therefore, that in these cases the product of bone-formation within the cartilage, the primary central spongy bone, is to a large extent absorbed and contributes only a small part of the mature skeleton. The early marrow-cavity, including all its ramifications between the trabeculæ, is filled with the young marrow-tissue; the latter becomes the red marrow that for a time fills the marrow-cavities of all the bones, and later is restricted to the spaces within the spongy bone tissue throughout the skeleton. It may be emphasized that the process sometimes spoken of as the "ossification of cartilage" is really a substitution of osseous tissue for cartilage and that, even in the endochondral mode of formation, cartilage is never directly converted into bone. Calcification of cartilage, however, occurs frequently in advanced age, and indeed is a constant phenomenon in certain cartilages, as in those of the larynx, beginning there at twenty to twenty-two years.

Depending to some extent on the shape and size of the bone to be formed, there are one or more centres of ossification In the bones of the carpus and tarsus there is but one centre for each bone. In the carpus the os capitatum is the first bone to show a centre; in the female at three months and eight days, in the male at seven months (Pryor, '25); while the os pisiforme is the last, the centre appearing in the female between the ninth and tenth year, and in the male between the twelfth and thirteenth year (Pryor, '16). These studies were made by the use of X–ray pictures, a method which has greatly facilitated the study of bone-growth, and these show that the process in the female is always in advance of that in the male. In the phalanges, metacarpals, and metatarsals there are usually two centres of ossification, one for the shaft and one for the epiphysis. In the long bones of greater size as the tibia and radius there are three centres, one for the shaft and one for the epiphysis at each end, and the centre for the shaft always appears before those in the epiphyses. Where there is still greater complexity, as in the femur, there are five or six centres. The time of first ossification is in the clavicle at the sixth fetal week. Other centres appear throughout fetal and postnatal life, some appearing as late as the eighteenth year, near the end of the growth-period.

Ossification within the epiphyses repeats in its essential features the details of intracartilaginous bone-formation as seen in the development of the shaft. After the establishment of the primary marrow-cavity and the surrounding spongy bone, ossification extends in two directions—towards the periphery and towards the adjacent end of the shaft. As this process progresses, the cartilage between the central spongy bone and the free surface soon disappears. As long as the growth continues, however, there persists between each epiphyseal centre and the spongy bone of the shaft, a mass of cartilage, which gradually becomes reduced to a thin plate and is termed the **epiphyseal plate** or **line.** This epiphyseal line at each end of the shaft is the important site of growth in length of the bone. As long as it persists it continues to proliferate, and simultaneously endochondral bone-formation replaces it with spongy bone both on the side towards the shaft and on the side towards the epiphysis. When, finally, due to a slackening in the formative activity of the cartilage, the bone-formation gradually encroaches upon it and entirely replaces it, the osseous tissue of shaft and epiphysis become continuous and growth ceases. In the tibia this occurs in the upper end at about eighteen and in the lower at nineteen to twenty years of age. At the extremities of the epiphyses which correspond to the later joint-surfaces, a narrow zone of cartilage persists over the spongy bone, and becomes the articular cartilage.

Periosteal Bone-Formation.—It is evident from the foregoing account of the development of bone within cartilage that the true bone-producing elements are contributed by the embryonic periosteum when the latter sends its processes into the ossific centre within the cartilage. The distinction, therefore, between endochondral and periosteal bone is one of situation rather than of inherent difference, as in the production of both the osteoblasts are the active agents and the essential features are identical.

Since in the development of periosteal or perichondrial bone the changes within cartilage do not come into account, the details are less complicated and concern primarily only a formative process.

The young periosteum consists of an outer compact **fibrous layer** and an inner loose **osteogenetic layer.** The latter is rich in blood-vessels and contains numerous embryonal connective tissue cells and delicate strands of fibres. Some of these cells become the osteoblasts and as such are arranged along the fibrillæ, about which the bone-matrix is deposited through the influence of the cells. The osseous trabeculæ, formed in this manner beneath the periosteum, increase in length by the addition of new matrix at the periosteum, and in thickness by the deposition of new layers of bone-matrix on the surface of the trabeculæ by the osteoblasts, some of these cells being surrounded by the matrix and thus converted into bone-cells. The spaces between the trabeculæ are occupied by the primary marrow, the direct prolongation from the periosteal tissue. During their further growth, the trabeculæ unite to form a subperiosteal bony network, the **peripheral spongy bone,** which surrounds the central spongy bone, or, where that has already disappeared, the central marrow cavity. Towards the ends of the shaft, where the cartilage still intervenes between the central spongy bone and the surface, the subperiosteal bone forms a thin perichondrial shell. The two processes, central and peripheral bone-formation, progress simultaneously, so that their products are often seen in the same microscopical field lying side by side, separated, however, by a thin and incomplete layer of calcified cartilage-matrix, known as the **boundary line.** From their relations to cartilage, it is evident that the periosteal bone never contains the remains of the calcified cartilage, while such enclosures are very common within the trabeculæ of the central spongy bone (Fig. 67).

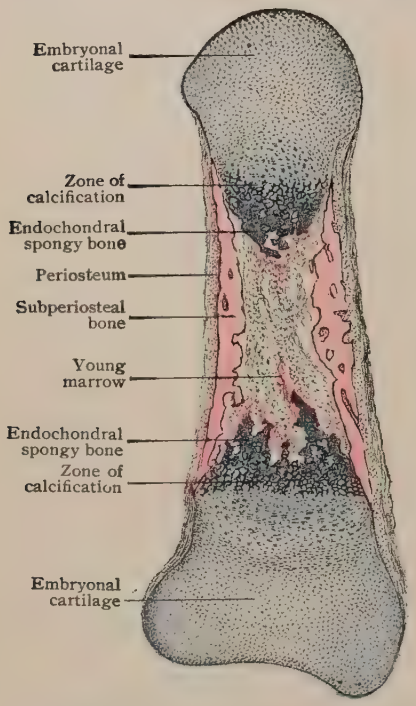


FIG. 66—Longitudinal section of phalanx of fetus of five months. × 23.

Formation of Compact Bone.—The conversion of the peripheral spongy bone into the typical compact bone of the shaft involves the partial absorption of the bony network and the secondary deposit of new osseous tissue. The initial phase of this conversion is the partial absorption of the trabeculæ by the osteoclasts within the primary marrow. As the result of this process, the robust and close reticulum of subperiosteal bone is reduced

to a delicate osseous framework enclosing enlarged marrow-channels. The latter are now known as the **Haversian spaces** and, in cross-section, are round or oval. After the destructive work of the osteoclasts has progressed to the required extent, the osteoblasts of the marrow-tissue within the Haversian spaces begin the formation of new bone on the walls of the spaces. This process is continued until, layer after layer, almost the entire space is filled with concentric lamellæ. The cavity remaining at the centre of the

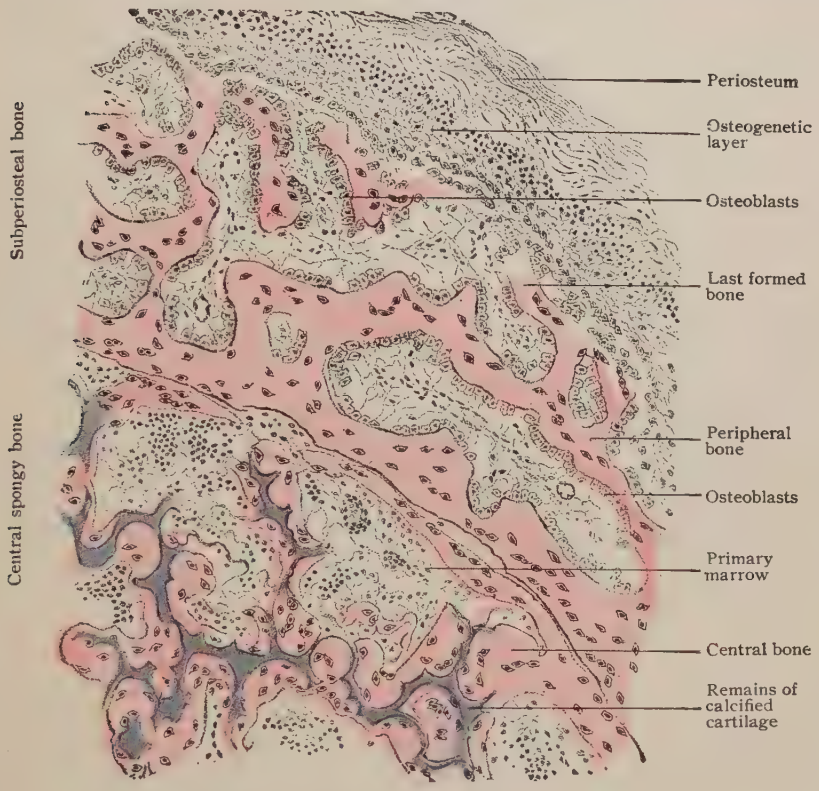


FIG. 67—Portion of developing humerus of fetal sheep, showing subperiosteal and central spongy bone. × 135.

former space persists as an Haversian canal, while the concentrically disposed layers of secondary bone are the lamellæ of the Haversian system, whose extent corresponds to the form and size of the Haversian space. The interstitial, or ground, lamellæ of adult bone are the remains of the trabeculæ of the primary subperiosteal spongy bone and are, evidently, genetically older than the Haversian lamellæ. The outer surface of the subperiosteal bone is beset with depressions occupied by the primary marrow-tissue. As these pits deepen in consequence of the increasing thickness of the growing bone, they are converted into the nutrient channels which occupy the circumferential and ground lamellæ. They are, therefore, not surrounded by

Haversian layers and correspond to the Volkmann canals, through which so many nutrient vessels enter the bone.

Intramembranous Bone-Development.—The bones constituting the vault of the cranium and the greater part of the face, develop within sheets of embryonal connective tissue. Except where developing muscle occurs, the early roof of the skull consists of the integument, the dura mater and an intervening stratum of young connective tissue. The latter layer contains numerous embryonal cells and delicate bundles of fibres. About the middle of the area corresponding to the later bone, some of these fibrous strands undergo calcification and thereby supply a radiating framework upon the surface of which the osteoblasts derived from the embryonal connective tissue cells, arrange themselves and bring about the deposit of bone-matrix. Delicate spicules of new bone radiate towards the periphery from the ossification centre thus established. As the trabeculæ increase in size and number they join to form a bony network, close and robust at the centre, and wide meshed and delicate towards the periphery where the osseous reticulum fades into the connective tissue. The details of this bone-formation by the osteoblasts correspond to those seen in other localities, including the conversion of some of the osteoblasts into bone-cells. With the growth of the bony tissue the network becomes more and more compact until it forms an osseous plate, which gradually expands towards the limits of the future bone. During this growth, the connective tissue covering the outer and inner surfaces of the plate assumes the character and arrangement of a periosteum and from the osteogenetic layer produces the compact surface lamellæ which enclose the intervening spongy tissue. This arrangement is seen in the fully developed bone (Fig. 55), where the so-called outer and inner tables enclose the diploë. The development of the superficial layers of the surface lamellæ is, therefore, identical with that of other subperiosteal surface lamellæ, while the production of the diploë corresponds with that of the peripheral spongy bone in its essentials, even to partial absorption in order to produce enlarged marrow-spaces. The secondary deposit of Haversian lamellæ, however, never takes place, the conspicuous systems of concentric layers being absent in the membrane-bones. Increased thickness of

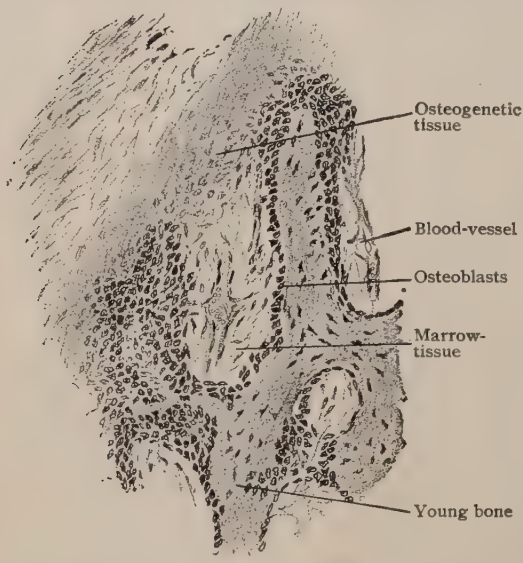


FIG. 68—Periphery of a developing membrane-bone (parietal), showing trabeculæ covered with osteoblasts. × 95.

the membrane-bones follows the addition of new surface lamellæ; increased area results from the marginal growth of the enclosed network of bony trabeculæ. In the young skull the vault-bones are separated by considerable tracts of connective tissue, conspicuous in the fontanelles and the evident sutures. This isolation continues, in principle at least, even after the bones are in close apposition and ends only with the complete replacement of the intervening periosteum by bone, such bony union being subject to great individual variations as to time and extent.

Growth of Bones.—Since new bone is deposited beneath the periosteum, it is evident that in a long bone such growth results in increased diameter of the shaft, as well as in increased thickness of the bony wall between the central medullary cavity and the surface. In order to maintain the balance between the longitudinal growth of the marrow-cavity (effected by the destruction of the cartilage and the absorption of the intracartilaginous bone) and its lateral expansion, removal of the innermost layers of the subperiosteal bone soon becomes necessary. This is effected by the **osteoclasts,** absorption of the older internal portion accompanying the deposition of new lamellæ on the surface. By this combination of destructive and formative processes, the thickness of the cylindrical wall of compact substance of the shaft is kept within the proper limits to insure the necessary strength without undue weight. During early growth, increase in the length of the bone at the ends is due to the addition of new cartilage formed by the perichondrium; later, these additions are supplemented by interstitial growth following multiplication of the cartilage-cells within the epiphyseal plates of cartilage. On attaining full growth and completed epiphyseal ossification, a portion of the cartilage persists as the covering of the articular surfaces. During the development of the short bones, in which the entire bone is made up by a mass of spongy substance enclosed by a shell of compact bone, no definite envelope of periosteal bone forms until the cartilage has been completely replaced by spongy bone. The subsequent growth and expansion of such bone is accomplished by the superficial addition of the periosteal bone. In the flat bones, as the scapula, the periosteal production is well advanced before the intracartilaginous process begins. In all bones after the cessation of peripheral growth, the osteogenetic layer of the periosteum becomes denser and much less rich in cells, although it retains an intimate connection with the last formed lamellæ by means of the processes which continue its tissue into the vascular channels within the bone. In addition to being the most important source of nutrition, on account of its blood-vessels, the periosteum responds to demands for the production of new bone, whether for renewed growth or for repair, and, when occasion requires, again becomes active as the chief bone-forming tissue, its cells reassuming the rôle of osteoblasts.

THE ARTICULATIONS

Broadly considered, the individual pieces composing the skeleton are united by articulations of two kinds: (1) the continuous joint (**synarthrosis**), in which the union is effected by uninterrupted masses of tissue and the

bones have no, or only very slight, play; and (2) the discontinuous joint (**diarthrosis**), in which the bones are joined by tissue containing definite joint-cavities and, therefore, are free to move on each other.

Synarthrosis may be: (a) by dense connective tissue (**sutura**), as in the immovable articulations of the skull, where the intervening periosteum is intimately connected with the bones by penetrating processes composed of white and elastic fibres; (b) by ligamentous tissue (**syndesmosis**) arranged in dense fibrous bands, which stretch between the adjacent bones and permit of slight movement, as between the lower ends of the tibia and fibula; and (c) by cartilaginous tissue (**synchondrosis**), which affords a rigid or flexible joint according to the proportions of the hyaline or fibrous varieties of the tissue. Thus, where the bond of union consists exclusively of hyaline cartilage, as between the component pieces of a young bone, immobility results; where fibrous cartilage predominates, as in the massive intervertebral disks, the union provides great strength and some flexibility. Outside the spongy substance or **nucleus pulposus,** which occupies the centre of the disk and is regarded as the modified remains of the chorda dorsalis of fetal life, the intervertebral disk consists of interwoven bundles of fibrous cartilage. Towards the surface the more typical cartilaginous tissue is replaced by a peripheral layer resembling tendon in structure.

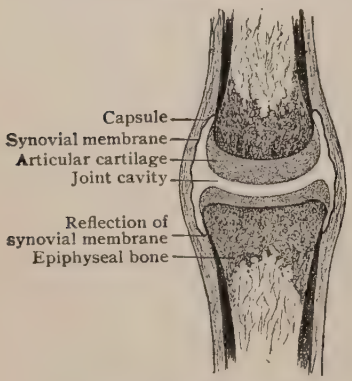


FIG. 69—Diagram showing essential parts of a typical joint.

Diarthrosis, or the true joint, includes, as its essential parts, the articular cartilage and the capsule; interarticular and adaptation cartilages and synovial tufts are secondary structures which may or may not be present. The **articular cartilage** covering the surfaces of the bones in apposition is, with few exceptions, of the hyaline variety. Next the joint-cavity, the cartilage-cells are usually flattened and arranged parallel with the free surface; deeper, the cells are more spherical in form and disposed in groups, while in the layers still nearer the underlying bone, the cartilage-cells often show a characteristic columnar arrangement, in which the rows of cells lie in a general way perpendicular to the surface of the bone. The matrix immediately overlying the bone is commonly the seat of more or less marked calcification, a zone of calcified matrix thus forming the union between the cartilage and the bone.

Where two joint-cavities exist, separated by an interarticular cartilage, the development of the partition, or **meniscus,** seems to influence the structure of the cartilage capping the articular surfaces of the bones. In such cases, as in the mandibular, costo-sternal, sterno-clavicular, acromio-clavicular, and lower radio-ulnar articulations, fibrous cartilage not only forms the interarticular plates, but also contributes the covering of the bones. Such instances, therefore, are exceptions to the usual investment of hyaline

cartilage. The adaptation cartilages, or **labra glenoidalia,** as the glenoid and semilunar cartilages in the shoulder and knee joint respectively, that serve to deepen the cups in which the humerus and the femur play, also consist of dense fibrous tissue containing rounded cartilage-cells.

The **capsule** surrounding the joint-cavity includes two layers: the outer fibrous and the inner synovial. The **fibrous layer,** made up of interlacing bundles of dense fibrous tissue, varies much in thickness in different joints, in the minute articulations between the ear-ossicles being a delicate membrane, while in the capsule of the hip-joint it reaches almost a centimeter.

The **synovial layer,** or synovial membrane, consists of loose connective tissue containing elastic fibres and more or less extensive groups of fat-cells; next the joint-cavity the tissue is condensed into a narrow compact stratum, whose free or joint-surface is clothed with flattened connective

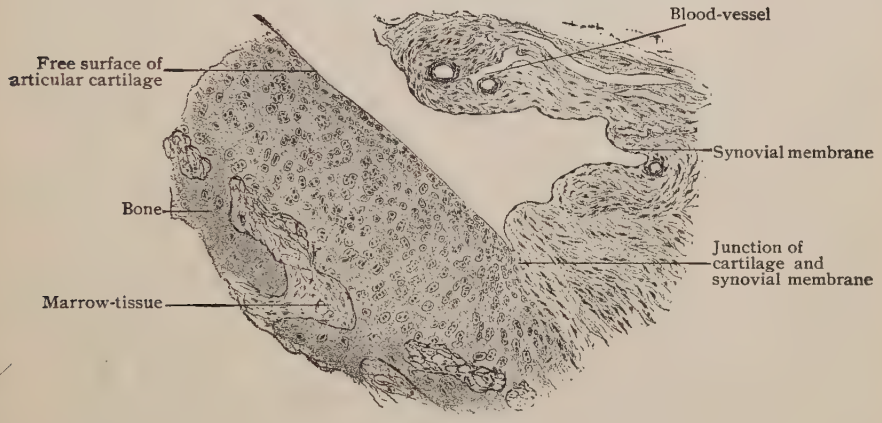


FIG. 70—Section through margin of joint, showing articular cartilage and synovial membrane. × 100.

tissue cells. The latter are plate-like elements and, where closely placed, form a lining for the capsule that resembles an imperfect endothelium. While the fibrous layer of the capsule is often carried for some distance beyond the margin of the joint to blend with the periosteum, the synovial layer is attached to the margin of the articular cartilage extending over the latter for a variable distance, but thinning out and disappearing over the surfaces subject to pressure. The actual articulating surfaces, therefore, are devoid of synovial membrane, the lubricated cartilages coming directly into contact during the movements of the bones.

Within the larger articulations the synovial membrane is thrown into folds, which project into the joint, enclose masses of adipose tissue, and are beset with numerous minute elevations. The latter, the **synovial villi,** are found especially around the margin of the articular surfaces and, in most cases, contain loops of capillary blood-vessels, which, together with the other capillaries within the synovial membrane, are important in producing the fluid within the joint. Although this synovial fluid, or **synovia,** consists almost wholly (94 per cent.) of water, it is slightly viscid and, therefore,

well adapted to lubricate the articulating cartilages. In addition to salts, protein and mucoid substances, the synovia contains oil drops and the remains of cells displaced by abrasion.

Blood-vessels and **nerves** are wanting within the articular cartilages as well as within the interarticular and the adaptation cartilages. The synovial membrane, on the contrary, possesses numerous vessels and nerves. The larger blood-vessels occupy the stratum of loose connective tissue, the capillaries penetrating into the innermost layer and the villi. The nerves include vasomotor and sensory fibres, some of the latter being connected with special endings (Vater-Pacinian bodies and Krause's articular end-bulbs). Definite **lymphatics** are found within the synovial membrane immediately beneath the joint-surface.

MUSCULAR TISSUE

Although possessed to some degree by all living protoplasm, contractility is exhibited characteristically by muscular tissue. The latter is made up of greatly elongated elements, which during contraction shorten in the direction corresponding with their long axes and, hence, exert a definite pull that results in movement. In the higher animals muscular tissue occurs in three chief kinds, the **voluntary striated,** the **cardiac striated,** and the **non-striated.** The first includes the muscles controlled by the will and hence the term **voluntary muscle;** the latter two act independently of volition and are **involuntary.** The nonstriated muscle represents the least specialized type. As an intermediate group stands the cardiac muscle, since this is beyond the control of the will, although it possesses striated fibrillæ. The highest degree of specialization of structure and function is shown by the voluntary striated muscles. The differences in structure of these three types are clearly reflected in the times required for a single contraction. In voluntary striated muscle the time is only 4/100 second, in cardiac muscle of the ventricle 3/10 second while in nonstriated muscle the contraction may last from three seconds to three minutes.

NONSTRIATED OR INVOLUNTARY MUSCLE

This variety of muscular tissue occurs in the form of bundles and thin sheets chiefly within the walls of the hollow viscera and of the vessels and,

FIG. 71—Involuntary muscle from intestine; several isolated fibre-cells are seen above. × 200.

although having a wide distribution in the body, seldom forms considerable masses. Its distribution includes: (1) The **digestive tract**—the muscularis mucosæ from the œsophagus to the anus and delicate bundles within the

mucosa; the muscular tunic from the lower half of the œsophagus to the anus; in the large excretory ducts of the liver, pancreas, and some salivary glands, as well as in the wall of the gall-bladder. (2) The **respiratory tract**—in the posterior wall of the trachea and as encircling bundles in the walls of the air-tubes. (3) The **urinary tract**—in the capsule and pelvis of the kidney and in the walls of the ureter, bladder, and urethra. (4) The **male reproductive organs**—in the epididymis, vas deferens, seminal vesicles, prostate and Cowper's glands, and cavernous and spongy bodies of penis. (5) The **female reproductive organs**—in the oviducts uterus, and vagina; in the broad and round ligaments; in the erectile tissue of the external genital organs and in the nipple. (6) The **vascular system**—in the walls of the arteries, veins, and larger lymphatics; sometimes in the trabeculæ of the larger lymph-nodes; in the capsule and trabeculæ of the spleen. (7) The **eye**—in the iris and ciliary region; in the eyelids (8) The **integument**—in the sweat and some sebaceous glands; in the minute erector muscles of the hair-follicles and in skin covering the scrotum and parts of the external genital organs.

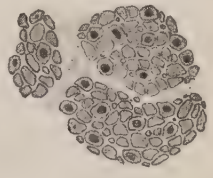


FIG. 72—Bundles of involuntary muscle in transverse section, showing the fibre-cells cut crosswise. × 400.

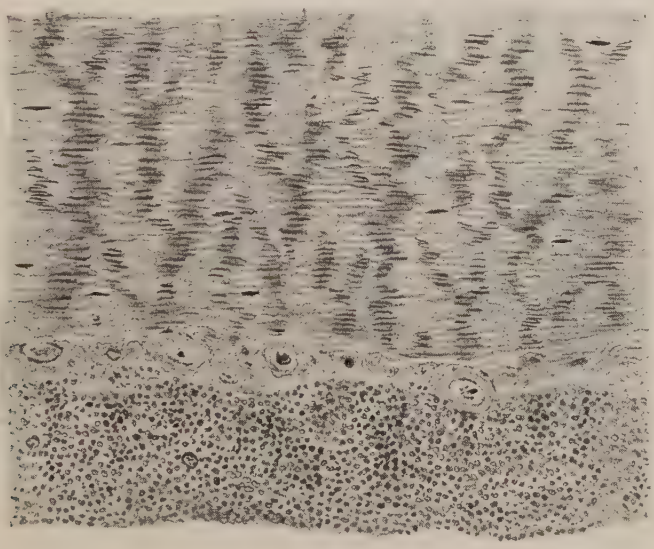


FIG. 73—Involuntary muscle of small intestine, in state of contraction. × 90.

Nonstriated, smooth, pale, unstriped, or involuntary muscle, as it is variously designated, consists of structural units known as the **fibre-cells.** These are delicate spindle, often prismatic, elements whose tapering ends fit between the adjacent fibre-cells. They vary greatly in size, measuring from 50–225 μ in length and from 3–8 μ in width. The fibre-cells found in the

skin and the blood-vessels are short (15–20 μ) and broad; those in the intestinal wall are more elongated (215–220 μ) and delicate. The largest elements are encountered in the gravid uterus where they may attain a length of 500 μ and a width of 30 μ. Each fibre-cell consists of protoplasm in which are embedded the **nucleus** and the **contractile fibrillæ**. The nucleus, usually described as rod-shaped from its elongated cylindrical form, is of nearly the same diameter throughout its length, and has rounded ends. It is rich in chromatin which usually presents a reticular arrangement. During contraction, the nuclei exhibit an active shortening and thickening, but with no change in volume (McGill, '09). The contractile fibrillæ are extremely delicate and are best studied at a magnification of 1000 or more, after suitable preparation. They run lengthwise in the fibre, and some continue from one fibre to another, forming intercellular bridges (McGill, '07). The larger fibrils often lie at the periphery of the fibre-cell, closely related to the denser **boundary zone,** which forms the exterior of the fibre-cell and fulfils the purpose of a limiting membrane, or sarcolemma, although no such definite structure encloses the smooth muscle-cell as in the case of the striated fibre.

FIG. 74—Portion of injected intestinal wall, showing arrangement of blood-vessels supplying involuntary muscle; upper layer longitudinally, lower transversely cut. × 50.

During contraction, as of the wall of the digestive tube, peristaltic waves pass along the muscular tissue. If smooth muscle tissue is fixed while still irritable the contraction waves are fixed and are seen to be due to nodal thickenings of small areas of adjacent muscle fibres (Fig. 73). These adjoining nodal points are often arranged more or less in lines, which stand out conspicuously even when viewed with low powers of the microscope. These nodal thickenings may be seen in isolated fibres, in both the fresh and fixed conditions. In some specimens it is seen that the nuclei are not straight, but are twisted and bent, and this is characteristic of the involuntary muscle in certain regions, as in the walls of arteries during contraction.

The individual fibre-cells are held together by an exceedingly delicate investment of connective tissue fibres, both white and elastic, which surround the muscle elements and in cross-sections appear as lines between the fibre-cells. Since the latter are fusiform, their transverse areas are relatively large when cut through the middle of the fibre-cell and progressively smaller towards the ends. The length of the nucleus being only a small fraction of the length of the fibre, it follows that in a cross section of a group of fibres, the nucleus will be seen in only a few of the fibres, viz.—in those which chance to be cut in their mid-region. (Fig. 72).

The **blood-vessels** supplying involuntary muscle, meagre in comparison with those of the striped muscle, are guided in their distribution by the septa of connective tissue in which the larger vessels run. These give off minute branches that terminate in capillary networks which extend between the primary bundles of fibre-cells. Numerous **lymphatics** likewise follow the larger septa of connective tissue. The **nerves** supplying involuntary muscle are sympathetic fibres. The larger trunks form plexuses, closely associated with microscopic ganglia, from which delicate twigs pass between the bundles of fibre-cells. Their ultimate relation with the contractile tissue is described with the Nerve-Endings.

CARDIAC MUSCLE

The contractile tissue constituting the greater bulk of the heart represents a type of muscle which, so far as histological differentiation is concerned, stands between the simpler smooth muscle and the highly complex striated tissue. The striking peculiarity of cardiac muscle, namely its reticular arrangement, is referable to embryonic conditions. The mesenchyma, from which the heart-muscle develops, for a time exists as a protoplasmic reticulum that contains irregularly distributed nuclei but is without distinct partitions across the bars of the network. This tissue corresponds, therefore, to a syncytium. As the syncytial network becomes more compact owing to the increasing width of its bars, or trabeculæ, with corresponding diminution of the intervening spaces, delicate contractile threads, the **myofibrils,** make their appearance within the reticulum and extend lengthwise through the trabeculæ, without regard to the limits of the areas marked out by the nuclei. Evidences of the primary reticular arrangement are seen in the characteristic networks formed by the adult cardiac muscle. These networks enclose long narrow meshes so that the trabeculæ show a more or less parallel arrangement.

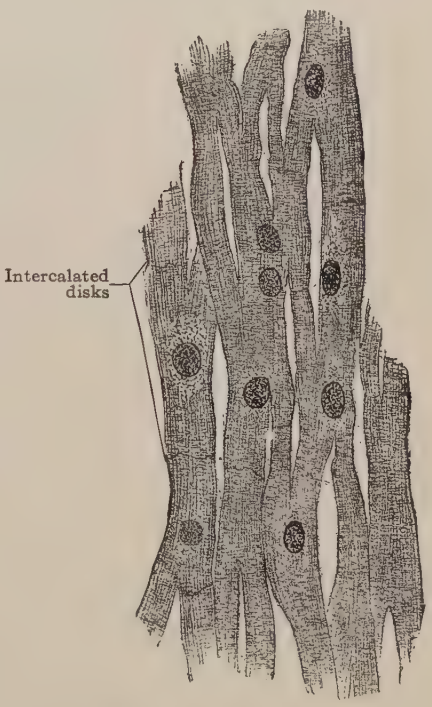


FIG. 75—Muscle trabeculæ of human heart. × 375.

This is best seen in sections passing parallel to the general course of anastomosing trabeculæ (Fig. 75). The latter consist of strands of delicately striated muscle in which lie oval nuclei. In cross-sections (Fig. 76), the

contractile fibrillæ are seen to be arranged in radiating lines which extend to the periphery of the trabeculæ but do not reach inward as far as the axis. The latter consists of a variable core of undifferentiated granular cytoplasm, or **sarcoplasm,** which surrounds the nucleus and usually contains a small quantity of pigment and fatty particles. In its general histological details, cardiac muscle agrees with typical striped muscle, the alternate light and dark stripes depending upon similar variations of density along the component fibrillæ. The probable significance of these markings will be considered under Striated Muscle; it will suffice here to indicate the peculiarities in which the muscular tissue of the heart differs from typical striated muscle. Although invested by a delicate sheath, the cardiac fibres do not possess a well defined sarcolemma. Their longitudinal striation, often very distinct, owing to the large amount of sarcoplasm between the groups of fibrillæ, is seemingly interrupted at intervals by dark transverse mark-

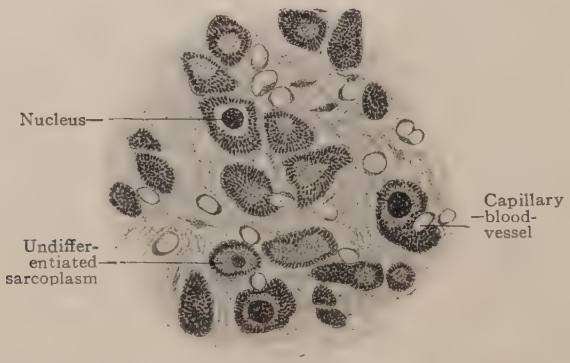


FIG. 76—Trabeculæ of cardiac muscle in transverse section. × 375.

ings, the **intercalated disks.** Examination of suitably prepared material, under high power, shows however, that the contractile fibrillæ do not suffer interruption, but are continued without break across the intercalated disks. Further, the disks do not always extend across the trabeculæ in the same plane, but may be step-like, or irregularly serrated. After dissociation reagents, such as a solution of caustic potash, heart-muscle breaks up into irregularly branched pieces, the so-called **fibres.** The lines of fracture correspond in position with the intercalated disks and, consequently, the ends of the isolated fibres often are not straight, but may exhibit a series of offsets like a serrated margin. The rhythmic repeated character of the contraction of cardiac muscle and its capacity for withstanding fatigue are important attributes of this variety of muscle. The latter may be associated in some way with the presence of a relatively large amount of sarcoplasm, for a similar condition is to be observed in the "red" voluntary muscles, in which a lower degree of differentiation seems associated with the power of enduring frequently repeated contraction.

STRIATED MUSCLE

The striped muscular tissue forms the conspicuous masses known as the "muscles" or "flesh" attached to the bony framework of the body. These organs are the active agents in moving the passive levers, the bones, and in producing the movements of the animal. The structural unit of voluntary muscle is the transversely striated **muscle-fibre,** which represents a highly specialized cell. The fibres are the contractile elements by whose shortening the length of the entire muscle is decreased and its force exerted.

The **muscle-fibres** are cylindrical, or prismatic with rounded angles in form and vary from .01–.1 mm. in diameter. No constant relation exists between the thickness of the fibres and the size of the muscle of which they are components, and, indeed, their diameter varies in the same muscle. The length of the muscle-fibres is likewise subject to great variation. As a rule, the fibres are of limited length, not exceeding from 4–5 cm.; in exceptional cases, as in the sartorius muscle, they may attain a length of over 12 cm. The fibres are usually slightly larger in the middle than at the ends, which are more or less pointed, but sometimes blunted or club-shaped or, rarely, branched. Branched and anastomosing fibres occur in the lingual, facial and ocular muscles.

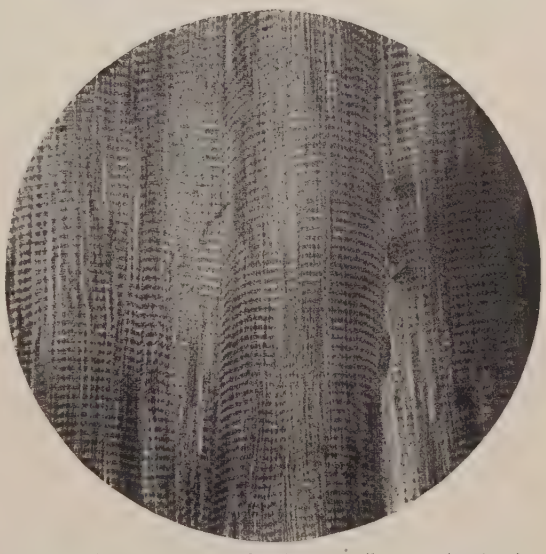


FIG. 77—Photograph of striated mammalian muscle, showing the usual appearance under moderately high magnification. × 700.

Each muscle-fibre corresponds to an enormously elongated multinucleated cell and consists of a sheath, or **sarcolemma,** and the contained **sarcous substance.** The sarcolemma forms a complete investment of the fibre and alone comes in contact with the surrounding connective tissue by which the muscle-fibres are attached to one another or to the fibrous structures upon which they directly exert their pull. The **sarcolemma** is a transparent, homogeneous, elastic membrane and envelops the contained sarcous substance so closely that, under ordinary conditions, it is almost or entirely invisible. Being tougher than the muscle-substance, it often withstands teasing with needles while the muscle is broken; where such breaks occur, the muscle-substance sometimes contracts within the sarcolemma, which then becomes visible at the fractures as a delicate tubular sheath (Fig. 79).

The **sarcous substance,** everywhere enclosed within the sarcolemma,

also consists of two parts, the less differentiated and passive **sarcoplasm** and the highly specialized **contractile fibrillæ** in which take place the active changes resulting in the contraction of the muscle-fibre. The characteristic cross-striation, resolvable into alternating light and dark bands, that distinguishes the fibres of voluntary muscle depends upon the constitution and arrangement of the contractile fibrillæ. These are threads of great tenuity which extend the entire length of the muscle-fibre and present series of alternating light and dark segments that probably correspond to differences of density. The dark denser areas are doubly refracting (**anisotropic**); the light less dense ones are singly refracting (**isotropic**). The cross-striation of the muscle-fibre as a whole results from the definite and orderly arrangement of the fibrillæ. Close lateral approximation of the denser and deeply staining segments of the fibrillæ, lying side by side within the sarcolemma, produces the impression of the dark band; the similar relation of the less dense and slightly staining segments produces the light band. The light band is subdivided by a delicate line, the **intermediate disk,** also known as **Krause's membrane.** In especially favorable preparations, the transverse disk appears less dense and lighter midway between its ends where it is traversed by a delicate line, the **median disk** (Hensen) or **middle membrane** (Heidenhain). The interpretation of these details, shown as ordinarily seen under moderately high magnification in Fig. 77 is still the subject of discussion. The intermediate disk, or membrane of Krause, is attached to the inner surface of the sarcolemma and extends completely across the muscle-fibre. This arrangement, however, does not imply that the fibre is composed of a series of separate discoidal segments, but rather that the membrane serves to maintain in definite order the contractile fibrillæ, which, while perhaps attached to the membrane, pass uninterruptedly through it.

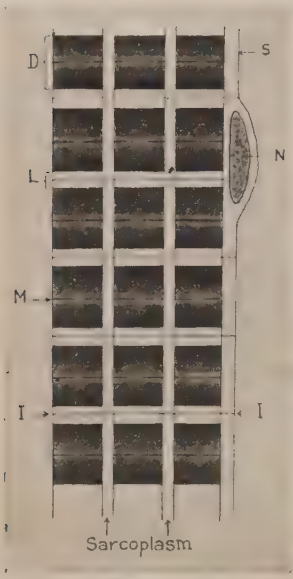


FIG. 78—Diagram illustrating structure of striated muscle cell. Three myofibrils of alternating dark (*D*) and light (*L*) substances; (*I*) intermediate membrane; (*M*) median membrane; (*N*) nucleus; (*S*) sarcolemma.

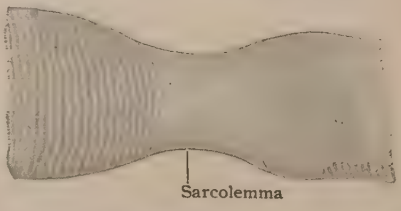


FIG. 79—Portion of muscle-fibre, showing sarcolemma bridging break in sarcous substance. × 370.

The distribution of the contractile fibrillæ within the fibre is not uniform, since the fibrillæ are grouped into minute bundles, the **muscle-columns,** or **sarcostyles.** This arrangement is shown in transverse sections of muscular tissue (Fig. 80), in which the individual fibres are seen to be made up of stippled areas separated by clear lines. These areas, known as **Cohnheim's fields,** represent the transversely cut groups of contractile fibrillæ, each area corresponding to a sarcostyle. The clear lines indicate the

distribution of the sarcoplasm between the fields of Cohnheim, each sarcostyle being entirely surrounded by the less highly differentiated substance.

Each muscle-fibre corresponds to a multinucleated cell. The numerous nuclei result from division of the nucleus of the embryonal cell, the **myoblast,** and remain embedded within the sarcoplasm as the **muscle-nuclei.** Their usual position in mammalian muscle is immediately beneath the sarcolemma; in certain fibres, however, as in the "red" fibres of the ocular and respiratory muscles, the nuclei lie more deeply embedded, therein agreeing in position with the nuclei in the muscles of many lower vertebrates.

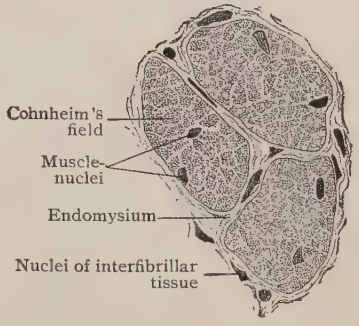


FIG. 80—Muscle-fibres of lizard in transverse section, showing fields of Cohnheim and muscle-nuclei. × 650.

The individual muscle-fibres, each invested in its sarcolemma, are grouped into small **primary bundles,** the component fibres of which are held together by a small amount of connective tissue, the **endomysium.** The latter is continuous with the envelope of the primary bundles, the **perimysium** (Fig. 81). The primary bundles are associated into uncertain groups the **secondary bundles,** which are united and surrounded by extensions and subdivisions of the general connective tissue sheath of the muscle, the **epimysium.** In muscles possessing a fine grain, the secondary bundles correspond with the **fasciculi,** but in muscles of coarse texture each fasciculus includes a number of secondary bundles.

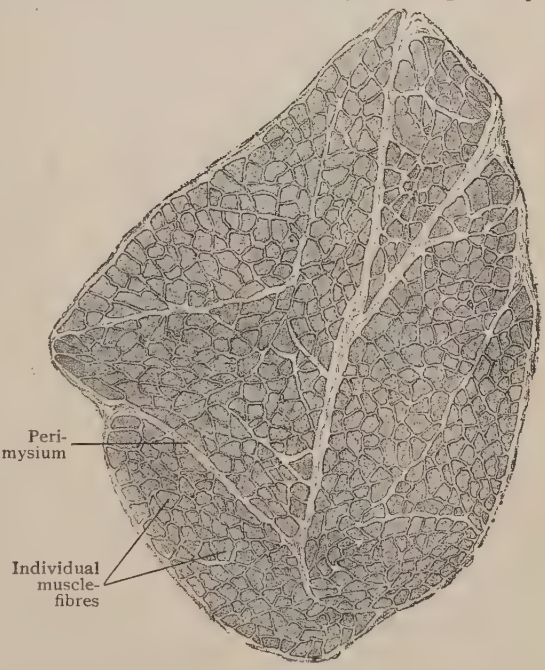


FIG. 81—Several primary muscle-bundles in transverse section, showing the arrangement of component fibres. × 40.

Although the skeletal muscles are usually pale in tint and contract energetically when stimulated, particular muscles of certain animals, as the semi-tendinosus and the soleus of the rabbit, exhibit a deeper color and contract more slowly and prolongedly under stimulation. Such **red muscles,** as they are called, are composed of fibres which are thinner than common and possess a relatively large amount of sarcoplasm, with nuclei

embedded not only beneath the sarcolemma, but also in deeper parts of the fibres (Fig. 82). Although not present in mammals generally in sufficient numbers to affect the appearance of entire muscles, the "red" fibres occur probably in all striated muscular tissue upon which devolves prolonged and frequently repeated effort. Such fibres, therefore, are present in the eye-muscles, and the muscles of respiration and of mastication. Possessing, as they do, a larger proportion of undifferentiated cytoplasm, the sarcoplasm, the red fibres are better able to withstand the fatigue of contraction. The pale fibres, on the contrary, gain in rapidity of contraction at the expense of early exhaustion.

The **blood-vessels** supplying striated muscle are very numerous. The larger arteries and accompanying veins enter the muscle along the connective tissue septa

FIG. 82—Portion of the soleus muscle of the rabbit in transverse section. The more coarsely stippled fibres are of "red" muscle; they also contain nuclei within the sarcous substance. × 160.

Longitudinal Transverse

FIG. 83 —Injected voluntary muscle, showing arrangement of interfascicular vessels and capillaries. × 50

and divide into smaller branches which run between the fasciculi. These vessels give off twigs which pass between the finer bundles of fibres and ultimately break up into dense capillary networks that surround the individual fibres with long rectangular meshes. The relation of the blood-vessels to cardiac muscle is exceptionally intimate, the capillaries not only enclosing the trabeculæ with rich networks, but also lying in grooves, or even in channels, surrounded by the muscular tissue. The **lymphatics** are represented by definite lymph-vessels which accompany the blood-vessels in the larger tracts of connective tissue. The **nerves** supplying striated muscle include both motor and sensory fibres. The former terminate in specialized end-arborizations, the **motor nerve-endings,** which lie beneath the sarcolemma and upon the sarcous substance. The sensory fibres are con-

nected with the neuro-muscular end-organs, or **muscle-spindles.** The description of both varieties of terminations will be found under the Nerve-Endings.

Development of Muscular Tissue—Muscular tissue is a derivative from the middle germ-layer with the exception of the involuntary muscle connected with the sweat-glands and the muscle-fibres of the iris, which apparently arise from the ectoderm. The voluntary muscles composing the skeletal group, however, arise from the modified mesoderm that forms the periphery of the quadrate areas, or **somites**, of the early embryo, while the tracts of involuntary muscle and the heart-muscle are developed from the mesenchyma. The details of their histogenesis vary in each case. Since **involuntary muscle** is the musculature of the viscera, it generally develops within the walls of tubes. Certain of the mesenchymal cells, the **myoblasts,**

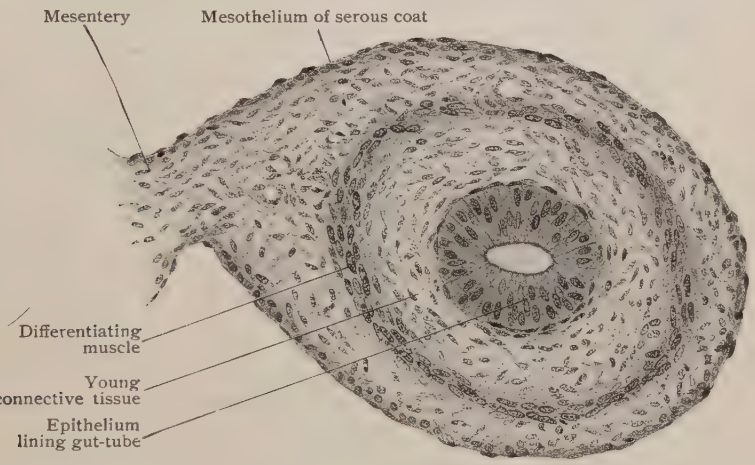


FIG. 84—Section of developing intestinal wall, showing differentiation of involuntary muscle from splanchnic mesoderm. × 180.

undergo proliferation and elongation and assume the characteristics of the fusiform fibre-cell. Their primary loose arrangement gives place to compactness with reduction of the intervening connective tissue.

The **cardiac muscle** originates from the nucleated protoplasmic reticulum, the syncytium, formed by the mesenchyma of the early heart-tube. Contractile threads, the myo-fibrils, make their appearance within the protoplasmic trabeculæ and increase in number by longitudinal splitting. The contractile fibrillæ are for a time homogeneous, but later undergo differentiation in density into alternating light and dark segments, which produce the general transverse striation of light and dark bands. The contractile fibrillæ are not uniformly distributed throughout the substance of the trabeculæ, but often appear grouped into narrow wedges, whose bases lie at the periphery of the fibre, with the thin edges towards the centre. The portion of the cytoplasm which is not converted into fibrillæ remains as an undifferentiated sarcoplasm, filling the intervals between the groups of contractile

threads. After the appearance of the intercalated disks (Fig. 75), the substance of the trabeculæ is subdivided into irregular areas, the so-called muscle-fibres, which by many are regarded as of questionable significance as true structural units. With the progressive increase in the muscular substance, the intertrabecular spaces and the contained embryonal connective tissue relatively diminish, the meshes of the network become very long and narrow, thus producing the appearance seen in definitive heart-muscle.

The **striated muscle** fibres arise from the greatly elongated myoblasts of the mesodermic somites. At first spindle-shaped and composed of granular cytoplasm, the embryonal cell increases rapidly in length, while its nucleus undergoes active proliferation, but for a time is devoid of all fibrillæ. These appear first in the periphery of the young muscle-cell and probably arise by fusion of linear rows of granules. They increase in number by longitudinal cleavage and are disposed in groups separated by the undifferentiated sarcoplasm. During the growth, the nuclei migrate from the interior to the surface of the fibre, where, beneath the sarcolemma already formed, they are found regularly arranged in the completely differentiated fibre, in which relatively little sarcoplasm remains. Coincident with the growth and increased number of the muscle-fibres, the intervening embryonal connective tissue becomes reduced to the meagre endomysium holding the individual fibres together, while that surrounding the primary bundles becomes the perimysium and the general muscle-sheath. During the early growth of the young muscle, actual increase in the number of fibres occurs, but thereafter, enlargement of a muscle is due chiefly to increased mass of the existing fibres owing to multiplication and lengthening of the fibrillæ.

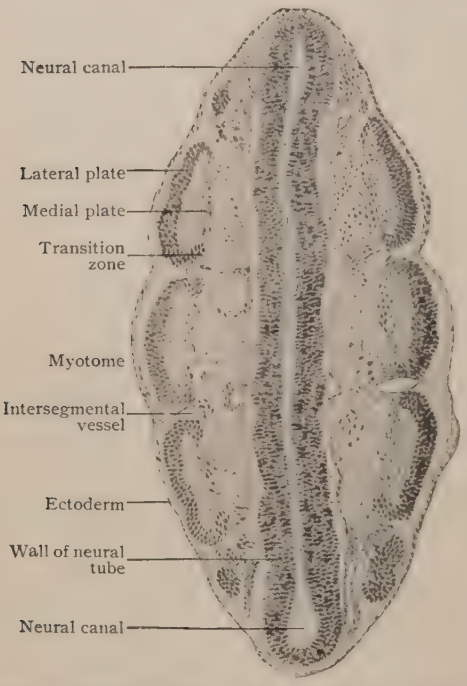


FIG. 85—Frontal section of rabbit embryo, showing myotomes. × 98.

Attachment of Muscles.—The attachment of the muscle fibres, whether to one another or to tendons, aponeuroses, periosteum, or fasciæ, is accomplished by the union of the fibrous attachments with the strands of connective tissue between the muscle-fibres and never directly with the sarcous substance. On joining a tendon, the pointed or obliquely ending fibres, each enclosed within its sarcolemma, are received between the tendon-bundles (Fig. 88) which fuse with the endomysium. A similar relation obtains where a

muscle is inserted into the periosteum or a fascia; but where the muscle is attached to the skin, the radiating muscle-fibres are continued by tendon-bundles of connective tissue rich in elastic fibres, an arrangement well-adapted to distribute evenly the pull of the muscle upon the integument.

The **aponeuroses** correspond in structure closely with the tendons, being composed of parallel bundles of dense fibrous tissue which are arranged to form membranous structures.

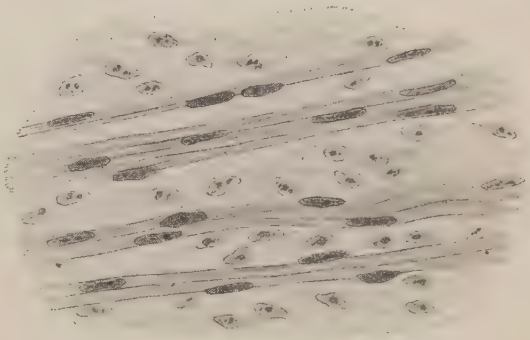


Fig. 86—Developing voluntary muscle; the fibres are still unstriated. × 525.

The **fasciæ** consist of feltworks of bundles of white fibrous tissue with a variable, usually considerable, proportion of elastic fibres. Where very dense, as in the fascia lata, they somewhat resemble tendon-tissue, the component bundles of fibro-elastic tissue being compactly disposed, although interwoven and lacking in uniform placing, and containing little fat. The superficial fasciæ, on the other hand, consist of loosely felted fibro-elastic strands and ordinarily support considerable, at times, very large masses of adipose tissue. Where the fascia serves as a muscle-sheath, it contains little fat but an unusual number of elastic fibres, by virtue of which it accommodates itself to the changing form of the enclosed muscular tissue.

Tendon-sheaths.—Where tendons play in bony grooves, or where it

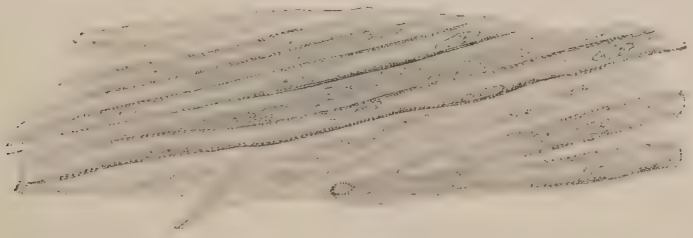


Fig. 87—Developing muscle fibres in which the striation is just appearing. × 375.

is necessary to overcome some tendency to displacement, they are bound down and held in place by bands of dense fibrous tissue, which either convert the grooves into canals or form tubular investments that enclose the tendons, although allowing free longitudinal movement. These connective tissue envelopes constitute the **tendon-sheaths** and may surround more than one tendon. Each sheath consists of an outer **fibrous tunic** (vagina fibrosa) composed of dense fibro-elastic bundles continuous with the periosteum at the margins of the groove, and an inner **synovial tunic** (vagina mucosa) which lines the deeper surface of the fibrous sheath and at the ends, or next

the bone, is reflected onto the tendon. The latter, therefore, is more or less completely surrounded by a double-walled cylinder, whose cavity is filled with a fluid serving to diminish friction during the play of the tendon. The synovial tunic resembles the lining of joint-cavities, being clothed with an imperfect layer of endothelial plates. In the larger sheaths, minute vascular projections recall the synovial villi.

Bursæ.—In situations in which a muscle or tendon moves over a bony prominence, or in which two tendons glide upon each other, the intervening areolar tissue contains a space filled with fluid, termed a **bursa.** Such bursæ, whose evident purpose is to diminish friction, are abundant in connection with the limb-muscles and in the vicinity of the large articulations may communicate with the synovial cavities. Conspicuous examples of such relation are the subscapular bursa, which opens into the shoulder-joint, and the suprapatellar bursa, which communicates with the cavity of the knee-joint. *Subcutaneous bursæ* are also developed in the areolar tissue separating the superficial and deep fasciæ in situations in which the skin glides over a bone and is subject to pressure, as over the tip of the elbow. The immediate lining of the bursal sac consists of an incomplete endothelial investment, while the wall of the sac itself is composed of dense fibro-elastic tissue.

Fig. 88—Section of tendon showing the termination of the muscle fibres. × 200.

NERVOUS TISSUE

All nervous tissues, whether in the central nervous system (brain and spinal cord) or in the peripheral nervous system are derived from the cells of the simple neural tube of the embryo. In their earliest stages these cells are rounded in shape, but by outgrowths of their cytoplasm they become transformed into elongated elements which extend varying distances. The processes of some cells remain within the walls of the neural tube, while the processes of others grow out into the body tissues and thus innervate all parts of the body. Such differentiated nerve-cells are called **neurones** and form the units of structure of the entire nervous system. The neurone consists of the **cell-body,** the mass of cytoplasm around the nucleus, and its **processes.** For the most part, the cell-bodies remain with the brain and spinal cord, but some migrate from the central axis to form peripheral ganglia. These collections of migrated cell-bodies form the sensory ganglia of the cranial and spinal nerves, and also the numerous ganglia of the sympathetic nervous system.

The nervous system, though exceedingly complex in its organization, is comprised of these relatively simple conducting elements, the neurones, arranged upon a definite plan. This plan may be first illustrated in the relation of the spinal nerves to the spinal cord (Fig. 89). A stimulus received

upon the skin passes along a sensory, or afferent, neurone, the cell-body of which is in a spinal ganglion, to the gray matter of the cord. Here it may pass into a motor, or efferent, neurone, the peripheral process of which leads to muscle-fibres. Reduced to its simplest form, this is the pathway by which an unexpected stimulus leads to a sudden muscular movement. This is the basis of a reflex arc. In addition, the sensory neurone has other branches which convey the stimulus along the spinal cord towards the brain. When this stimulus by passing through other neurones, reaches the appropriate centre in the brain, a sensation is felt. If there is an injury of the pathway in any part of its course which prevents the impulse reaching its destination, the normal sensation does not ensue.

Thus the peripheral nervous system consists of sensory, or afferent, and

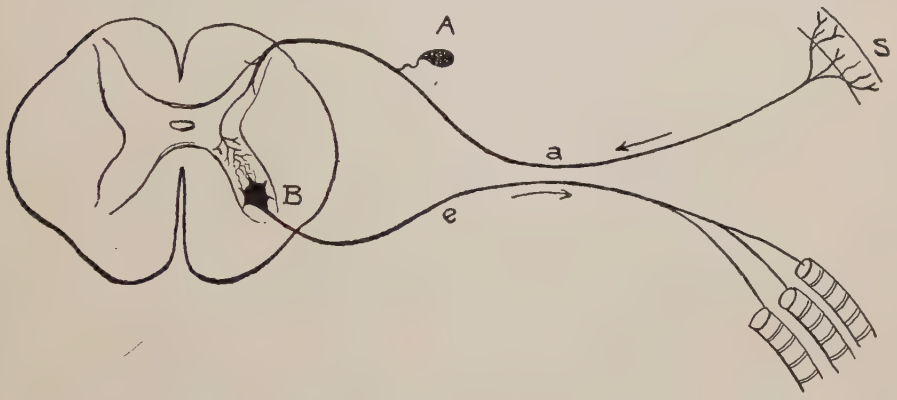


FIG. 89—Diagram showing fundamental units of nervous system. *A*, sensory neurone, conducting afferent impulses by its process (*a*) from periphery (*S*); *B*, motor neurone sending efferent impulses by its process (*e*) to muscle.

motor, or efferent, neurones. Similarly, the neurones conveying stimuli towards the higher centres are known as afferent, and those carrying impulses away from the higher centres as efferent.

In the central nervous system the neurones are supported by a special sustaining tissue, the **neuroglia,** and in the peripheral nervous system fibrous connective tissue forms the supporting tissue.

The Neurones.—As before stated, the neurones consist of the cell-body (nerve-cell) and its processes. The latter, as seen in the case of a typical motor neurone extending from the spinal cord to a striated muscle, are of two kinds: (a) the branched protoplasmic extensions, the **dendrites,** which are usually multiple and form elaborate arborescent ramifications that establish relations with other neurones within the gray matter of the ventral horn, and (b) the single, unbranched **axone** (neuraxis, neurite) which leaves the spinal cord and extends to the muscle as one of the components of a spinal nerve.

The **dendrites** are usually uneven in contour and robust as they leave the cell-body (nerve-cell), but rapidly become thinner in consequence of their repeated division, until they are reduced to delicate threads that

constitute the terminal arborizations, the **telodendria,** formed by the end-branches. The dendrites collect and carry impulses toward the cell-body: the axones carry impulses away from the cell-body. The **axone,** slender, smooth and of uniform thickness, is much less conspicuous than the dendrites. It may be short, extending only to nearby cells, or it may be of great length, connecting distant parts that lie, either wholly within the cerebro-spinal axis (as from the brain-cortex to the lower part of the spinal cord) or extend beyond (as from the lower end of the spinal cord to the plantar muscles of the foot). On reaching its destination, the axone terminates in an end-arborization, or telodendrion. In the case of axones terminating in muscles, these telodendria take part in the formation of the motor-nerve endings which will be described later. Where an axone is one of a series forming a pathway, the axonal telodendrion comes into close contiguity with the dendritic telodendrion of the next neurone in the series, but there is no direct continuity. This relationship is known as a **synapsis,** or **synapse.** In the passage of nerve impulses along a pathway, the synapses appear to be regions which retard the rate of progression of the stimulus. According to Cajal's theory of sleep, unconsciousness supervenes when these telodendria retract, and the usual stimuli cannot pass across the intervening gaps. By these telodendria one axone may carry impulses to the dendrites of a number of neurones, and conversely, the dendrites of one neurone may receive impulses from the axones of several other neurones. Neurones are divided according to the distribution of their axones into two classes. In those of the first class, known as **type I cells,** the axone is continued as a nerve-fibre and is, therefore, relatively long. Soon after leaving the cell-body (nerve-cell), such axones give off delicate lateral processes, the **collaterals,** which after a longer or shorter course, break up into arborizations that end in relation with other and often remote neurones. The neurones composing the second and much less frequent class, **type II cells,** possess

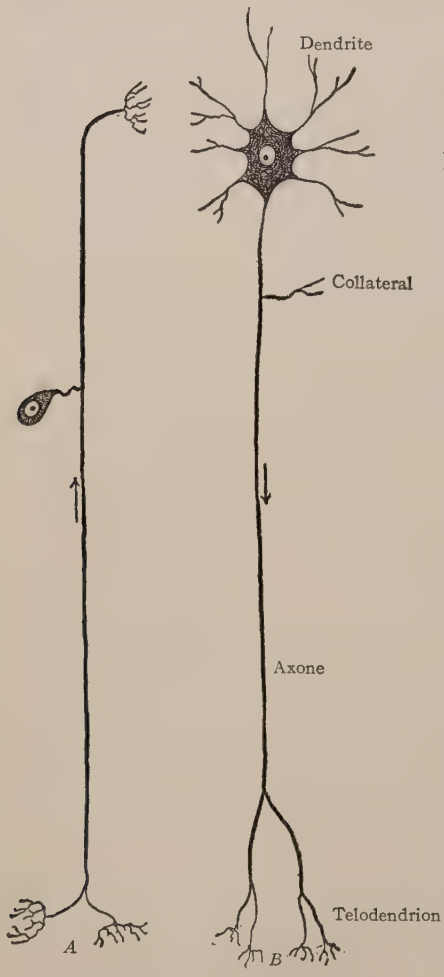


FIG. 90—Diagram of typical neurones. *A*, sensory; *B*, motor.

short axones that are not continued as nerve-fibres, but almost immediately break up into complex end-arborizations, or **neuropodia,** limited to the gray matter.

The **nerve-cells,** as the cell-bodies of the neurones commonly are called, are in general relatively large elements, those in the ventral horns of the spinal cord measuring from 70–150 μ. They possess a large spherical nucleus poor in chromatin but usually provided with a conspicuous nucleolus. Their cytoplasm varies in appearance with the method of fixation and staining to such an extent, that some uncertainty exists as to the relation of many described details of the actual structure of the living cells. It is probable, however, that the cell-body of the neurone consists of a homogeneous *ground-substance* or **hyaloplasm** in which fine **neurofibrils** and masses of

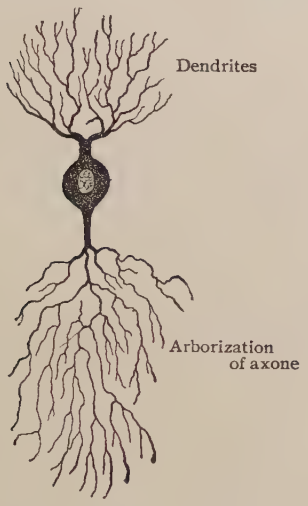


FIG. 91—Diagram of nerve cell of type II, in which axone is not prolonged as nerve-fibre.

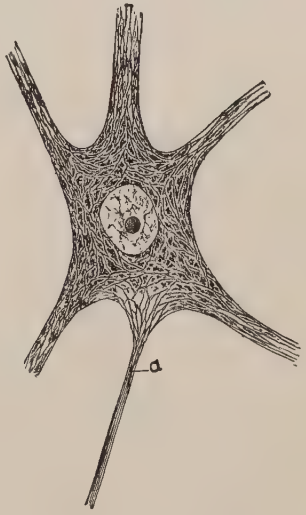


FIG. 92—Semidiagrammatic representation of structure of neurone; *a*, axone.

chromatophilic granules are embedded; in addition a variable amount of brown or blackish **pigment** is usually present in the vicinity of the nucleus. The neurofibrils are continued into all the processes as far as the terminal arborizations. After special staining as with methylene blue, the chromatophilic granules appear deeply colored and grouped in variable masses, known as **Nissl bodies,** which occupy the interstices of the fibrillar reticulum. Collectively the granules of "stainable substance" constitute the **tigroid substance** and are most conspicuous in the neighborhood of the nucleus and least so at the periphery of the cell. They are continued into the dendrites as elongated flakes that finally resolve into scattered granules along the processes. The axone, on the contrary, does not contain Nissl bodies and usually joins the cell-body at an area free from the stainable substance, the process usually arising from a slight elevation known as the **implantation cone.** Exceptionally, the axone arises from one of the dendrites, either at its

base or at some distance from the cell-body. Owing to the size of the cells, little more than the stumps of the processes are ordinarily seen in sections.

Depending upon the number of their processes, neurones are described as **unipolar, bipolar,** or **multipolar.** The **unipolar neurones** occur only among the lower vertebrates, the apparent examples seen in the familiar cells composing the spinal and other ganglia connected with sensory nerve-fibres resulting from secondary changes. Primarily, such neurones possess an axone and a dendrite, which pass from the opposite ends of the young oval cell. During development, however, the unilateral growth of the cell-body brings about the gradual approximation of the two processes until they fuse in the single extension into which the flask-shaped cell is prolonged.

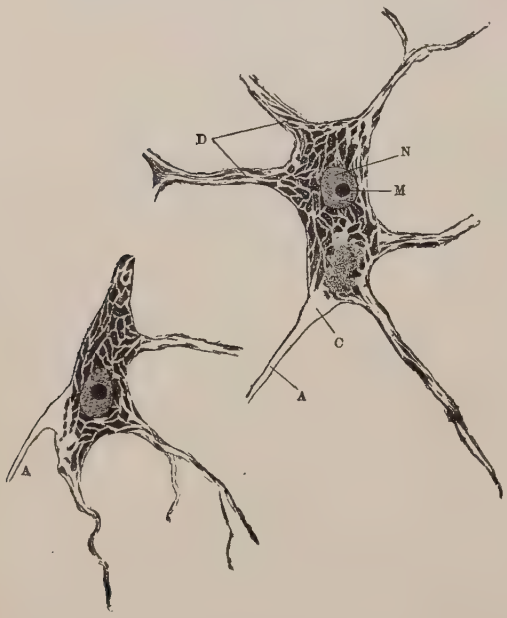


FIG. 93—Nerve cells of human spinal cord stained to show Nissl bodies; *A*, axones; *C*, implantation cone; *D*, dendrites; *N*, nucleus; *M*, nucleolus. × 400.

Examples of **bipolar neurones,** in which the dendrite and axone pass from opposite sides of the cell-body are found in the retina and the ganglia connected with the acoustic nerve. An interesting modification of bipolar neurones is presented by the olfactory cells within the nasal mucous membrane, whose dendrites are represented by the short microscopic processes whilst the axones are prolonged as the fibres of the olfactory nerves towards the olfactory bulb of the brain.

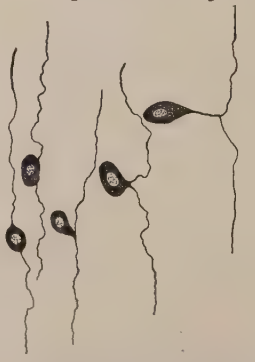


FIG. 94—Diagram showing transformation of young bipolar sensory neurone into one of unipolar type.

FIG. 95—Bipolar neurones; *a*, from olfactory mucous membrane—the dendrite is above; *b*, from retina. (*Cajal*).

The cell-bodies of the **multipolar neurones,** which possess one axone and several dendrites vary in form. Some, as those within the sympathetic ganglia, are approximately spherical and of moderate size, with short delicate dendrites; many are of large size and irregularly stellate form, the dendrites passing out in all directions, as seen in the conspicuous motor neurones within the ventral cornua of the spinal cord; others possess a regular and characteristic outline, as the flask-shaped

cells of Purkinje within the cerebellum or the pyramidal cells of the cerebral cortex. Certain multipolar neurones within the cerebral cortex, and especially those constituting the chief components of the granule-layer

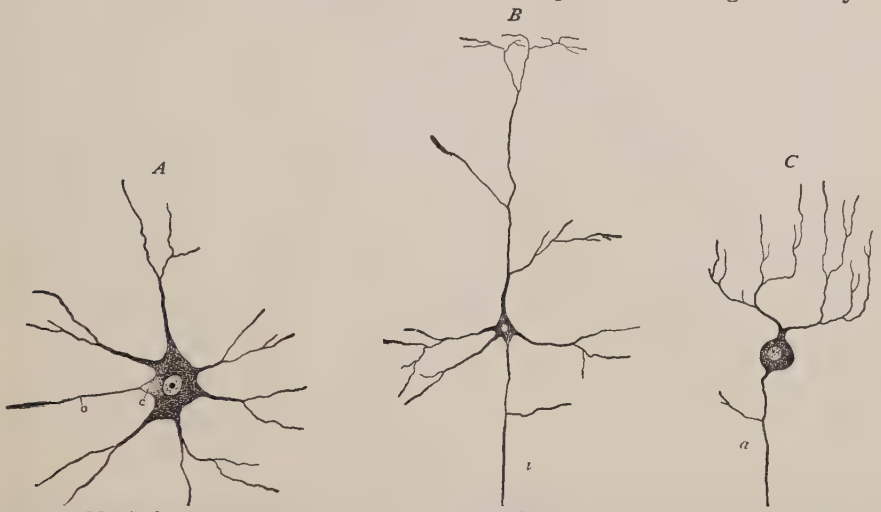


FIG. 96—Multipolar nerve cells of various forms; *A*, from spinal cord; *B*, from cerebral cortex; *C*, from cerebellar cortex; *a*, axone; *c*, implantation cone.

of the cerebellum, are distinguished by the small size of their cell-bodies and the peculiar ramifications and claw-like telodendria of their dendrites. Within the cerebellar cortex are also found examples of multipolar neurones of type II, whose axones almost immediately undergo branching within the gray matter to which they are confined.

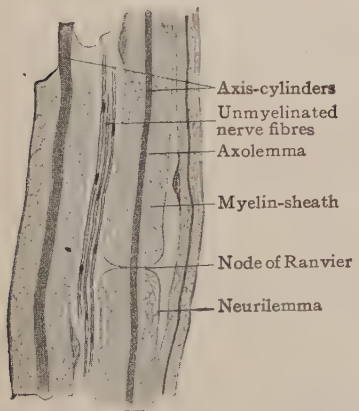


FIG. 97—Myelinated and unmyelinated nerve-fibres, as seen in longitudinal section of spinal nerve. × 375.

The Peripheral Nerve-Fibres.—From what has been said above, it is evident that nerve fibres are not independent elements but only the processes of neurones—either

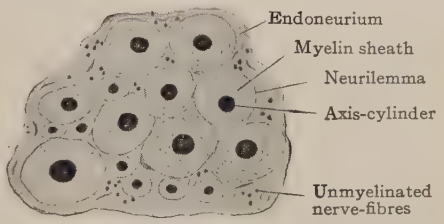


FIG. 98—Myelinated and unmyelinated nerve-fibres in tranverse section. × 385.

the axones from cell-bodies within the spinal cord or in sympathetic ganglia, or the dendrites of cell-bodies situated within the ganglia of the spinal and cranial sensory nerves.

The fundamental part of every nerve-fibre is the central cord, known as

the **axis-cylinder,** which is composed of delicate threads, the **axis-fibrillæ,** prolonged from the nerve-cell and embedded within a semi-fluid interfibrillar substance, the **neuroplasm.** In the case of the fibres, which form the most conspicuous constituents of the peripheral nerves, the axis-cylinder is surrounded by a relatively thick coat, known as the *medullary,* **or myelin sheath,** outside of which lies a thin structureless envelope, the **neurilemma,** or *sheath of Schwann.* These coverings, however, do not invest the entire nerve. Thus, for a short distance after leaving the nerve-cell, the axis-cylinder is without covering; soon it becomes surrounded by the myelin sheath, and then, if it be a peripheral nerve, acquires the outer envelope, the neurilemma. In the case of the nerve-fibres that course within the brain and spinal cord, the fibre is devoid of the neurilemma, although it usually possesses the myelin sheath. Conversely, not all nerve-fibres in the peripheral nerves possess myelin sheaths, although all are provided with neurilemma cells.

The *medullary,* or **myelin, sheath** consists of two parts, a delicate reticular **framework** and a fatty substance, the **myelin,** that fills the meshes of the supporting reticulum. The former arranged for the most part as connected membranous lamellæ, resists pancreatic digestion and fat-dissolving reagents and is composed of a substance named **neurokeratin.** The reactions exhibited by myelin indicate its fatty nature, this substance existing during life perhaps in the form of an extremely fine emulsion supported by the framework. When fresh, myelin appears clear and highly refracting, and confers the characteristic whitish color upon the nerve-fibres which it covers, "medullated, or myelinated, fibres" as they are called. It is prone to post-mortem changes, so that after death it loses its former uniformity and presents irregular contractions and collections, or extrudes in irregular globules at the ends of the broken fibres. The myelin sheath is not uniformly continuous, but is almost completely interrupted at regular intervals marked by annular constrictions. These constrictions, the **nodes of Ranvier,** correspond to very narrow zones at which the myelin sheath is practically wanting and the neurilemma dips in and comes into close relation with the axis-cylinder. The myelin sheath, however, does not suffer complete suppression at the nodes, but is represented by a part of its framework which traverses the constrictions. The latter occur at regular intervals along the fibre which they thus divide into a series of **internodal segments.** In a general way, the segments are longer (about 1 mm.) in large fibres, and shorter in those of small diameter, in which they are reduced to .1 mm. or less in length. The axis-cylinder passes uninterruptedly across the nodes and is continuous from its origin in the nerve-cell to its ending in the terminal arborization, or telodendrion. The neurilemma also suffers no break at the nodes, but continues from one segment to the other. After treatment with osmic acid, the myelin sheath frequently appears broken by clear narrow lines that extend obliquely from the neurilemma towards the axis-cylinder, and thus subdivide each internodal segment into a number of smaller

tracts, known as the **Schmidt-Lantermann segments.** These clear, narrow lines indicate the position of the thicker unstained funnel-shaped lamellæ of the neurokeratin. Within each internodal segment in the neurilemma lies an oval elongated nucleus, the **neurilemma nucleus.** Thus the neurilemma of one segment with its nucleus probably represents a single tubular cell, wrapped around the nerve-fibre. These cells represent the continuance of the ectodermic elements (**sheath cells**) that were active during the growth of the nerve-fibre in providing its envelope.

According to the presence or absence of the myelin coat throughout the greater part of their course, nerve-fibres are designated as **myelinated** or **unmyelinated** (medullated or non-medullated). The **myelinated fibres** constitute the greater mass of those making up the peripheral nerves and the fibre-tracts within the cerebro-spinal axis. The fibres within the latter, however, although myelinated are without a neurilemma. The **unmyelinated fibres** of the peripheral nerves, on the other hand, are chiefly prolongations, post-ganglionic fibres, from the ganglion-cells of the sympathetic system. In the case of the olfactory nerves the fibres are unmyelinated and also without a neurilemma. The distinction between these two classes of nerve-fibres, however, is relative rather than absolute, since every myelinated nerve-fibre becomes unmyelinated not only at its origin from the cell, but also before making its terminal arborization, whether central or peripheral. Myelinated nerve-fibres vary from 1–20 μ in thickness. According to their diameter, they are grouped as *fine* (1–4 μ), *medium* (5–9 μ) and *coarse* (10–20 μ). In a general way it may be said that the thicker fibres are the longer and are the processes of large nerve-cells; conversely, the finer fibres are shorter and belong to small cells. Although subject to many exceptions, the efferent, motor fibres are usually the thicker, and the afferent, sensory, the thinner.

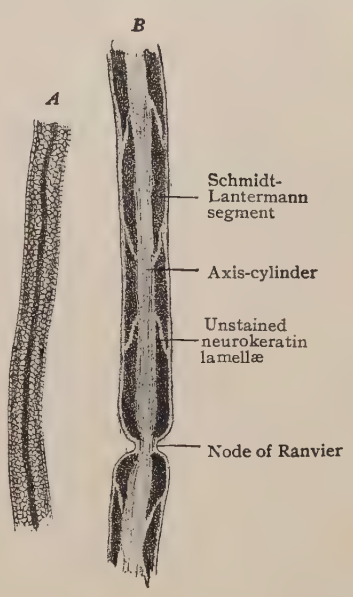


FIG. 99.—Myelinated nerve-fibres after treatment with osmic acid; *A*, fibre showing reticulum within myelin coat; *B*, one showing same coat divided into segments. × 500.

Since there are many more peripheral nerve-fibres than nerve-cells, it is evident that the former must undergo division along their course. Such doubling occurs always at a point corresponding to a node of Ranvier, never within an internodal segment, the sheaths being continued on the resulting fibres. On approaching their peripheral termination, the branching becomes more frequent and the myelin sheath thinner until it ceases, after which the axis-cylinder continues covered by only the attenuated neurilemma. The

latter, now reduced to an extremely delicate covering beset with occasional nuclei, sooner or later disappears, the naked axis-cylinder alone being thence prolonged to end finally in the varicose threads of the telodendrion. The

FIG. 100—Unmyelinated nerve-fibres in longitudinal section of splenic nerve. × 310.

unmyelinated nerves proper, also termed the *pale fibres* or *fibres of Remak*, include those that are devoid of the myelin sheath throughout their course. Such fibres are chiefly the axones of sympathetic neurones. They are often 2 μ or less in diameter and consist of only the axis-cylinder and the neurilemma, the latter being thin and delicate. The pale fibres, like others, end in terminal arborizations composed of naked axis-cylinders.

Neuroglia.—The neurones (nerve-cells and nerve-fibres) within the brain and spinal cord are everywhere held together by a special supporting tissue known as neuroglia. The latter is derived primarily from the ectoderm which forms the wall of the neural tube, certain elements, the **spongioblasts,** being concerned in the production of the neuroglia, while others, the **neuroblasts,** give rise to the neurones. For a time the supporting tissue is represented by greatly elongated, radially disposed fibre-cells that often extend the entire thickness of the wall of the neural tube. Later, the neuroglia elements become differentiated into: (a) those bordering the lumen of the canal, where they are partially retained as the **ependymal cells;** and (b) those which early migrate to more peripheral positions and give rise to stellate **gliogenetic cells** that are converted into spider-like elements (Fig. 101). In chrome-silver preparations these appear as irregular triangular or quadrilateral cells from whose angles extend the numerous delicate **fibrillæ** that later become the chief constituents of the neuroglia. So long as neuroglia is being produced, the gliogenetic cells are present and concerned in the production of additional fibrillæ, their cytoplasm becoming progressively reduced until in their final condition of the small **glia cells,** little more than the nucleus remains. During these changes very many fibrillæ lose their connection with the cells and, in conjunction with the glia threads still attached, form an intricate interlacement in which the neuroglia cells, now greatly reduced and for the most part devoid of processes, lie scattered at uncertain intervals.

FIG. 101—Young neuroglia cells; astrocytes from brain of child. × 300.

The mature neuroglia everywhere consists of essentially the same tissues, the differences noted in certain localities depending largely upon variations in its compactness. Its chief constituent is the intricate feltwork

of **glia-fibres** which are usually free but to some extent connected with the glia-cells. Where, however, the neuroglia borders the brain-ventricles and the central canal of the spinal cord it presents special features. In these situations it forms the **ependyma,** which appears as a single-layered epithelial lining. Within the cord, the cells are pyramidal, their bases looking towards the lumen of the tube and their apices towards the nervous tissue. At least during the earlier years in man, and throughout life in many lower animals, the free surfaces of the cells are beset with hair-like processes resembling the cilia of epithelial cells. The pointed distal ends of the ependymal cells are prolonged into processes continuous with neuroglia fibres that are soon lost in the surrounding glia-complex. Where the ependyma lines the ventricular spaces, the cells are low cuboidal elements that constitute a continuous and single-layered investment, whose primary relation to the surrounding neuroglia is often lost.

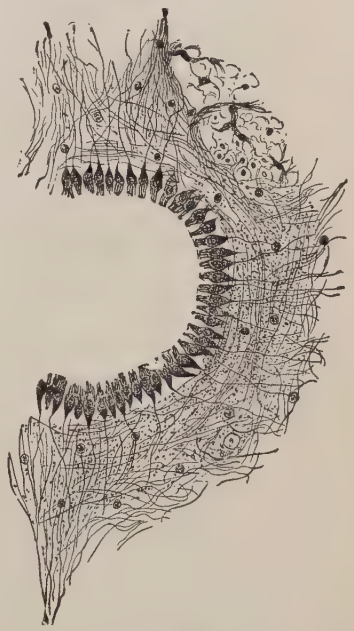


FIG. 102—Ependymal cells and adjacent neuroglia surrounding central canal of spinal cord of cat. × 75. (*Rubaschkin.*)

The Nerve-Trunks.—The component fibres of the peripheral nervous system are assembled into larger or smaller cords, the "nerves" of gross anatomy, which extend to various parts of the body. Those that supply both muscles and sensory surfaces (integument or mucous membranes), as, for example, the median or the mandibular nerve, include three sets of nerve fibres: (1) the efferent axones of the motor neurones, whose cell-bodies are situated within the spinal cord or the brain-stem; (2) the afferent dendrites of sensory neurones within the spinal or cranial sensory ganglia; and (3) the efferent axones of neurones within the sympathetic ganglia that accompany the spinal fibres to the periphery for the innervation of involuntary muscle in blood-vessels and skin, of glands, and of the skeletal muscle.

The nerve-fibres, the representatives of the three sets usually more or less intermingled, are grouped into bundles, the **funiculi,** which differ in number and diameter, according to the size of the entire trunk that they form. Each funiculus is surrounded by a definite sheath of dense connective tissue, the **perineurium,** which is continuous with the delicate fibro-elastic tissue prolonged as the **endoneurium,** between the individual nerve-fibres. Where well developed, the sheath of the funiculus consists of concentric fibrous lamellæ, between which are the **perineural tissue-spaces.** The latter are in relation with the tissue-clefts between the nerve-fibres on the one hand, and with the lymphatics within the interfunicular tissue on the other. When, as usually is the case, the nerve is made up of several funiculi, these

are loosely bound together and the entire nerve-trunk so formed is invested by a general connective tissue envelope, the **epineurium,** in which lie the

FIG. 103—Transverse section of small nerve-trunk composed of loosely united funiculi. × 20.

larger blood-vessels and the lymphatics. These coverings of the nerve-trunk are continued over its branches, even over its smallest subdivisions. The

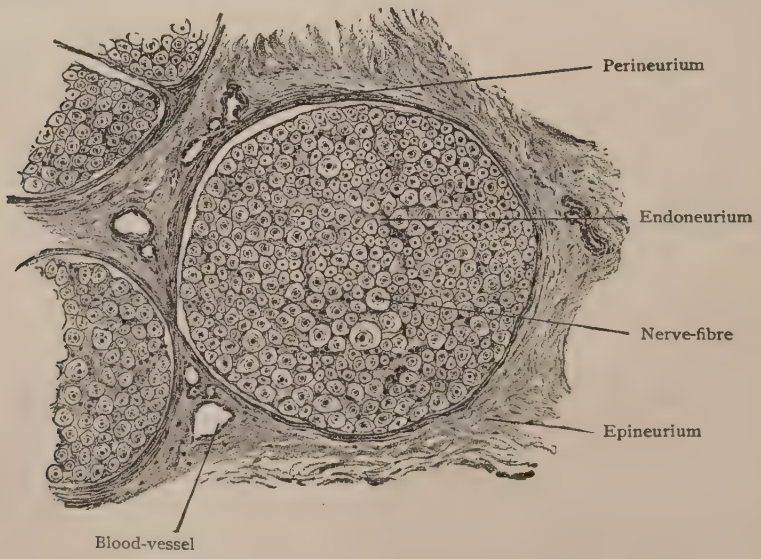


FIG. 104—Transverse section of funiculus composed of nerve-fibres held together by endoneurium and surrounded by perineurium. × 175.

last representative of these envelopes is prolonged over the individual nerve-fibres as the **sheath of Henle,** which lies outside the neurilemma and consists of flattened cells and delicate strands of connective tissue.

In cross-sections of the nerve-trunk (Fig. 104), the transversely cut individual myelinated nerve-fibres appear as small circles, sharply defined by a fine outline, the neurilemma, each enclosing a deeply stained dot, the axis-cylinder in section; the interval between the latter and the neurilemma corresponds to the space occupied by the myelin and neurokeratin and usually appears clear and unstained, with the exception of delicate septa of the neurokeratin. In contrast with the foregoing appearance, is that seen after the action of osmic acid or special hematoxylin staining (Weigert), the myelin substance then exhibiting a dark color and appearing as a deeply tinted ring which surrounds the axis-cylinder. The neurilemma-nuclei are occasionally seen as deeply stained crescentic figures that partly encircle the nerve-fibres, lying beneath the neurilemma. Viewed in cross-sections, the unmyelinated fibres appear as small irregularly round fields arranged in groups that correspond to bundles. When numerous, the latter are aggregated into secondary bundles between which extend delicate septa of connective tissue continuous with the general envelope of the nerve-trunk. The fibres being unmyelinated, their diameter is very small, sometimes less than one micron.

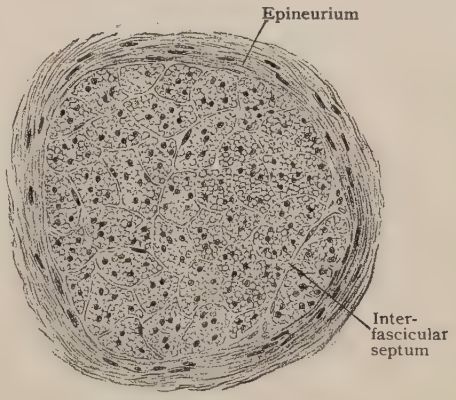


FIG. 105.—Transverse section of small splenic nerve consisting chiefly of unmyelinated fibres. × 180.

The Ganglia.—The cell-bodies of the neurones constituting the sensory, or afferent, paths within the peripheral nerves, as well as those within the sympathetic, or visceral, nerves, are collected into aggregations known as ganglia. Familiar examples of the latter are the spinal ganglia on the dorsal roots of the spinal nerves, certain cranial ganglia (as the semilunar, or Gasserian, connected with the fifth nerve, the acoustic with the eighth, and those on the trunks of the seventh, ninth, and tenth cranial nerves), and the sympathetic ganglia along the gangliated cords and within the plexuses of the sympathetic.

A longitudinal section of a **spinal ganglion** (Fig. 106), which may be taken as a type of such collections, shows the entire ovoid mass to be surrounded by a *fibrous capsule*, continuous with the epineurium ensheathing the nerves. Immediately beneath the capsule, the ganglion-cells are disposed in a fairly continuous layer of varying thickness, while the more deeply placed cells are broken up into groups by the tracts of nerve-fibres, a small amount of connective tissue prolonged from the endoneurium of the nerve-bundles and accompanying the blood-vessels being also present. The majority of the ganglion-cells are from 60–80 μ in diameter, but some measure as much as 170 μ and others as little as 25 μ. In sections they usually appear round or oval, since only exceptionally in ordinary preparations are their

processes to be seen. Each nerve-cell is surrounded by a *capsule*, lined with flat cells. The nervous elements may be grouped into *large cells*, whose axones give rise to myelinated nerve-fibres, and *small cells*, whose axones continue as unmyelinated fibres. Depending largely upon the behavior of their axones, Dogiel has described eleven types of nerve-cells of the spinal ganglia. Sympathetic fibres also are present.

The **sympathetic ganglia** correspond in their general structure with those situated on the spinal nerves. They are enclosed by a fibrous capsule,

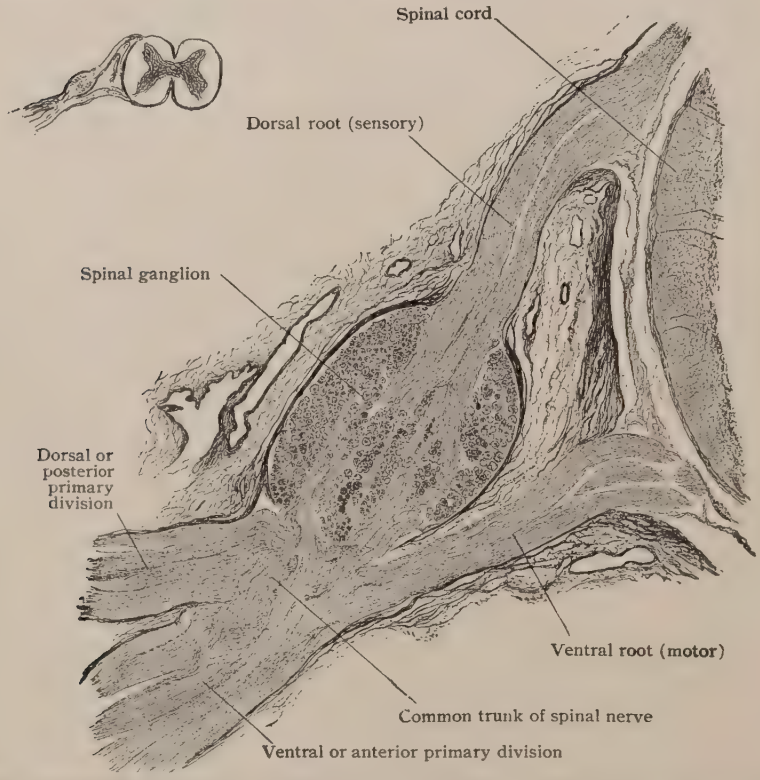


FIG. 106—Section of spinal nerve, showing its roots, ganglion, common trunk and primary divisions. × 9.

from which prolongations of connective tissue pass into the interior of the ganglion for the support of the nervous elements. The individual ganglion cells, in mammals always multipolar, are surrounded by nucleated capsules continuous with the neurilemma of the nerve-fibres. Many of the ganglion cells give off sympathetic efferent axones, which, as unmyelinated fibres, join the splanchnic trunks and end in the involuntary muscle of the various internal organs and in the glands. Other neurones send axones, by way of the gray rami communicantes toward the periphery of the body to be distributed, generally by paths following the cerebro-spinal nerves to skeletal muscles and to the involuntary muscle within the walls of the blood-vessels,

to the sweat glands, and the skin. Among the cells of the sympathetic ganglia often are mingled dendrites, that are traversing the splanchnic paths as afferent fibres, conveying sensory impulses from the viscera, to reach the ganglia on the dorsal roots and, eventually, the reception nuclei of the spinal cord. Although the axones of the sympathetic neurones for the most part are devoid of myelin sheath, and appear as pale fibres, this condition often applies only to part of their course. The spinal efferents, which join the sympathetic by way of the white rami communicantes, are myelinated fibres. Eventually, they too, lose the myelin-sheath and, after a variable course as unmyelinated fibres, end in arborizations composed of naked axis-cylinders that surround the sympathetic ganglion cells.

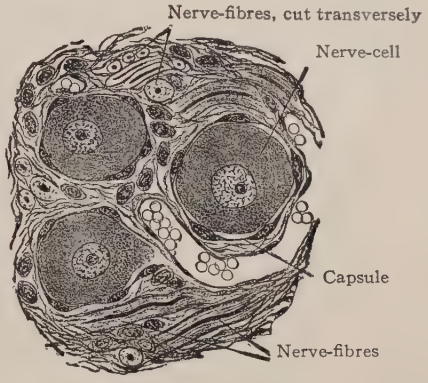


FIG. 107—Section of spinal ganglion showing nerve-cells surrounded by nucleated capsules. × 300.

Under the **paraganglia** are included clumps, or cord-like collections, of cells which are derived from the formative areas of the sympathetic ganglia and share with cells scattered throughout the sympathetic nerves and

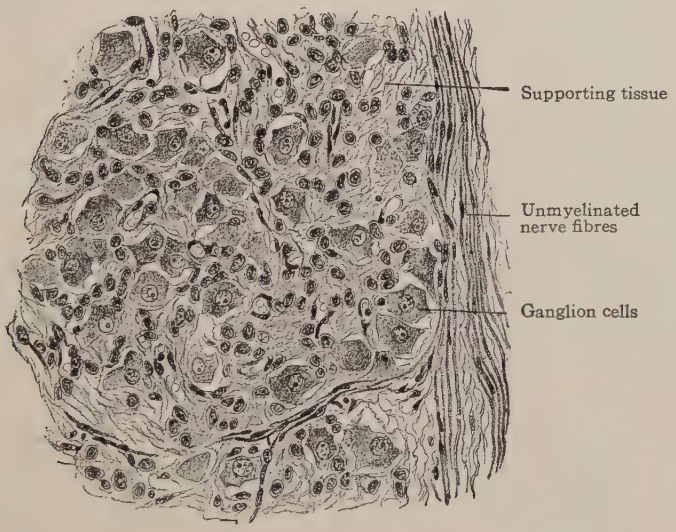


FIG. 108—Portion of section of sympathetic (semilunar) ganglion from child. × 250.

ganglia the peculiarity of being stained yellowish brown by solutions containing chromic acid or chromium salts. In recognition of this affinity, these elements are known as **chromaffin cells** and regarded as related to the sympathetic system. Definite collections of such cells, associated with a complex of blood-vessels along the course of large arteries, occur in the carotid and aortic bodies, as well as within the medulla of the suprarenal body.

DEVELOPMENT OF THE NERVOUS TISSUES

Although the reader must be referred to the larger and special books for a systematic and detailed description of the development of the nervous system, an understanding of the chief features of its histogenesis is so important for an appreciation of

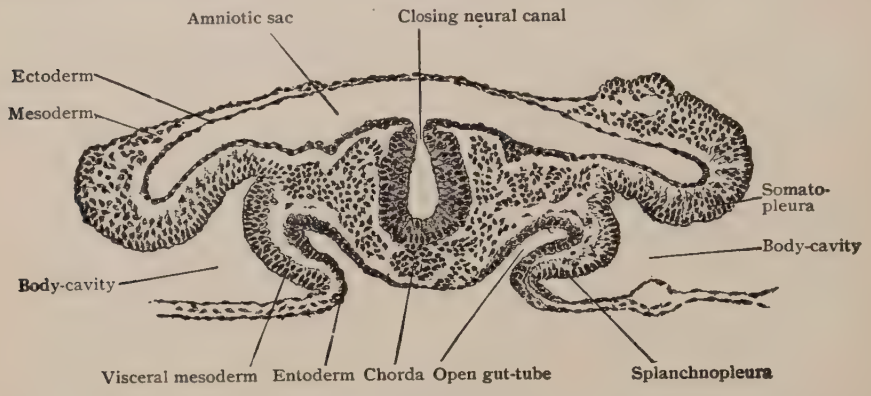


FIG. 109—Transverse section of rabbit embryo of about nine and one quarter days. × 80. Neural canal is just closing.

the relations of its structural components that a sketch of these processes finds here an appropriate place.

Among the very earliest phases of the embryo is the formation of a longitudinal furrow, the **neural groove,** bounded by thickened ectoderm and corresponding with the long axis of the embryo. By the approximation and fusion of its dorsal lips, this groove is gradually converted into a closed tube, the **neural canal.** The walls of this canal, from which all the essential nervous elements are derived, consist at first of only a few layers of the invaginated ectodermic epithelial cells. The latter actively proliferate and become converted into a multinucleated tissue in which the cell-boundaries disappear and the nuclei lie embedded within a general protoplasmic tract, or **syncytium.** The larger dividing elements, the **germinal cells,** conspicuous on account of their mitotic figures, lie close to the lumen of the tube. Soon this continuity is interrupted by the appearance of spaces within the syncytium, the cell-substance being resolved into a delicate reticulum, the **myelospongium.** The meshes of the reticulum enlarge, the intervening nucleated tracts elongate, and the increasing nuclei become radially disposed. Following these changes, the elements next the lumen assume a columnar form and radial arrangement and become the **primary ependymal cells,** while the remaining elements, the **indifferent cells,** increase by the continued division of the germinal cells. The indifferent cells later differentiate into the **spongioblasts** from which the characteristic constituents of the neuroglia are derived, and the **neuroblasts** which are directly converted into the neurones.

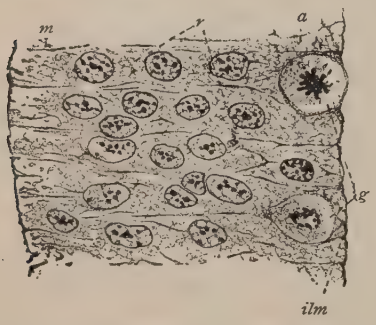


FIG. 110—Segment from lateral wall of neural tube of pig embryo of 5 mm.; syncytium replacing distinctly outlined cells. *a*, inner zone; *g*, germinal cells; *ilm*, internal limiting membrane; *m*, peripheral zone; *r*, radial strands of cytoplasm. × 690. (*Hardesty*).

The **neuroglia** is evolved by the gradual transformation of the spongioblasts and their descendants into fibrillæ and the production of a more definite framework that replaces the primary myelospongium and eventually, in conjunction with the processes

derived from the ependymal cells, gives rise to the completed supporting tissue. The **neurones** are directly derived from the neuroblasts. The latter are distinguishable from the spongioblasts as soon as they are provided with nerve-processes. These appear as outgrowths from the peripherally directed and pointed ends of the developing nerve-cells. The first, and for a considerable time the only, processes which the motor neurones possess correspond to axones that become the axis-cylinders of efferent (motor) nerves.

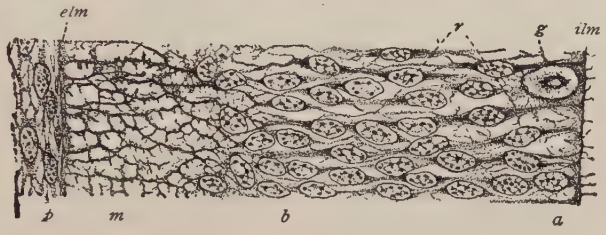


FIG. 111—Segment of wall of neural tube of pig embryo of 10 mm.; radial strands (*r*) of syncytium and differentiation of ependymal (*a*), nuclear (*b*), and marginal (*m*) layers; *ilm*, *elm*, internal and external limiting membrane; *g*, dividing cell; *p*, pia mater. × 690. (*Hardesty.*)

Subsequently the dendrites grow out in various directions from the cell-bodies of the young neurones.

The **peripheral nerves** according to the embryological studies of His and the experimental work of Harrison, are outgrowths from the nerve-cells, since the axis-cylinder of the entire nerve-fibre is formed by the peripherally directed growth of the original nerve-process of the neuroblast. The motor neuroblasts within the spinal cord and the sensory cells within the spinal ganglia send out processes of considerable thickness, which give rise at their extremities to groups of fibrillæ. These increase in thickness and length and,

FIG. 112—Transverse section of part of developing spinal cord from pig embryo of 30 mm.; *c*, central canal; *ep*, ependymal layer; *n*, nuclear layer; *m*, marginal layer; *r*, radial fibres. × 240. (*Hardesty*).

in turn, at their extremities give rise to new groups of fibrils. The latter proceed at first as naked bundles, but soon become surrounded by the **sheath-cells,** which are of ectodermic origin, and enclose the young developing nerve. After a nerve has become enlarged by the distal ingrowth of fibrils, the sheath-cells wander from the periphery among the fibrillæ, and thus give rise to a network that divides the original fasciculus into a number of secondary bundles. The interfascicular cells increase rapidly, the subdivision continues and the bundles of fibrillæ become progressively smaller and more compact until, surrounded by membranous septa, they become the **axis-cylinders** of the individual nerve-fibres, enclosed by the **neurilemma** and its cells. The **endoneurium**

appears comparatively late and, unlike the neurilemma, is a product of the mesoderm. Later condensations of the mesodermic tissue around the definite bundles of nerve-fibres

FIG. 113—Portion of spinal cord of human embryo, showing development of ventral root axones as outgrowths from ventral neuroblasts. × 300. (*After His.*)

and around the entire nerve-trunk provide for the **perineurium** and the **epineurium,** respectively. The **myelin sheath** is acquired comparatively late, since it does not appear until about the fourth month of fetal life. Some tracts within the central nervous axis, indeed, do not obtain the myelin coat until after birth. It is probable that formation of the myelin is in some way influenced by the axis-cylinder, resulting in the deposit of the myelin droplets from the fluid that surrounds the axial thread.

FIG. 114—Cross-section of part of dorsal region of human embryo, showing development of spinal ganglion; *d z*, *v z*, *m z*, dorsal, ventral, and marginal zones of early spinal cord; *dr*, *vr*, dorsal and ventral root-fibres of spinal nerve (*sn*); *sg*, spinal ganglion on dorsal root. × 75.

The **sensory ganglia** develop from groups of ectodermic cells that form a ridge, the **ganglion-crest,** on the margin of either lip of the still open neural tube, just where the general ectoderm passes into that lining the groove. On closure of the latter, the ganglion crests fuse into a dorsal wedge-shaped mass that becomes a centre of proliferation from which cells migrate outwards over the dorso-lateral wall of the tube. In consequence, a series of segmentally arranged cell-aggregations appears on each side of the neural canal, these collections being the rudiments of the spinal ganglia. Within them certain cells soon become fusiform, and assuming the rôle of neuroblasts, send out a process from each end. One process, the axone, grows centrally, while the other, the dendrite, extends peripherally and becomes the chief part of a sensory neurone, the afferent nerve-fibre. The subsequent growth of the neurone is not symmetrical, but to one side, so that the two processes approximate and, finally, join the cell-body by a common stalk, the neurone being thus converted into an unipolar ganglion-cell. The centrally directed processes, later the dorsal root-fibres of a spinal nerve, grow into the developing cord and enter the immature white matter to end, when development is complete, at various levels in

relation with the neurones within the gray matter of the cord and some ascend to the medulla oblongata (nucleus gracilis and cuneatus). The peripherally directed processes, on the other hand, mingle with the axones from the motor neurones to form the mixed nerves distributed to the various parts of the body. The essential parts of the sensory neurones, the cell-body and the processes, are derivatives of ectodermic elements, while the investing sheaths, whether of the whole nerve-trunk or of the entire ganglion, are contributions of the mesoderm.

The **sympathetic system** shares with the spinal ganglia a common origin from the primary ganglion-crest. As the latter differentiates, certain immature cells separate and migrate ventrally toward the vicinity of the aorta; along this path of migration later appear groups of cells, foreshadowing the ganglia of the ganglionated cord. Meanwhile, neurones of the spinal cord, send axones along the ventral spinal roots and into the developing sympathetic strand, eventually to end around the sympathetic cells and so bring, by way of the white rami communicantes, the sympathetic elements under the influence of the cells of the spinal cord. Before marked segmentation of the ganglionated cord occurs, thickenings appear from which bundles of sympathetic efferents grow mesially to form the prevertebral ganglia; subsequent migration into the developing viscera establish the terminal ganglia. The neurones of the ganglionated cord send axones peripherally, thus contributing the gray rami, which carry sympathetic efferents to the outlying involuntary muscle of the blood-vessels, and skin, and to the glands.

NERVE-TERMINATIONS

The termination of the fibres composing the peripheral nerves—the axones of certain motor neurones situated within the cerebro-spinal axis and within the sympathetic ganglia and the dendrites of the neurones within the sensory ganglia—supply the apparatus by which the various structures are brought into intimate relation with the central nervous system. Some of these terminations convey impulses that produce various sensations (pain, pressure, muscle-sense, temperature); others transfer impulses resulting in muscular contractions. The nerve-terminations, therefore, may be grouped according to function into **sensory** and **motor endings.**

Sensory Nerve-Endings

Since the sensory endings are the more or less modified terminal arborizations of neurones whose cell bodies lie within the spinal and other sensory ganglia, such terminations are functionally the beginnings of the paths conducting sensory stimuli to the central nervous system. According to their relations to the surrounding tissue, the sensory endings are broadly grouped into **free** and **encapsulated.**

Free Sensory Endings.—These endings include numbers of nerve-terminations found in the skin and the mucous membranes, chiefly within the epithelium but to some extent also within the connective tissue, and between the fibres of voluntary muscle. As a rule the sensory, afferent, nerve-fibres branch only to a limited degree until near their peripheral destination, where they undergo repeated division, always at a node of Ranvier and in various directions. The myelin coat of the main fibre is retained until close to its termination, although some of its branches may course as unmyelinated fibres for a considerable distance before ending or entering the epithelium. In the skin—and the same general plan applies to the mucous membranes—the fibres destined for the epidermis lose their myelin

coat beneath the epithelium which they enter as vertically coursing unmyelinated fibrils. Within the epithelium they break up into delicate fibrils which undergo further division into still finer varicose threads that ramify between the deeper epithelial cells and terminate in free end-knobs. Similar, but far less numerous free endings varicose and club-like in form, occur within the connective tissue layers of the skin and mucous membranes. Conspicuous ramifications of sensory fibres surround the hair-follicles, lying upon the outer surface of the glassy membrane.

FIG. 115—Free sensory endings within epidermis of rabbit; in several places nerve fibrillæ terminate in end-knobs. (*Dogiel.*)

Encapsulated Sensory Endings.—In their most highly developed forms, these endings, corpuscula nervorum terminalia, are represented by large special end-organs in which the terminations of the axis-cylinder are enclosed within an elaborate laminated capsule. The latter, however, is more often present as a much simpler and thinner envelope consisting of strands of connective tissue.

Transitional forms between the intraepithelial tactile cells above noted and the more specialized end-organs, always within the connective tissue seen in the **corpuscles of Grandry** (not found in man, but conspicuous in the skin covering the bill of many water-fowl), in which the ramifications of the nerve-fibrillæ end within a disk-like mass, the **tactile disk** enclosed between large modified epithelial elements, the **tactile cells.**

The group of simpler encapsulated end-organs includes three well-known examples: the **tactile corpuscles,** the **end-bulbs,** and the **genital corpuscles.**

The Tactile Corpuscles.—These bodies, also called the **corpuscles of Meissner,** are most numerous in the corium of the skin covering the flexor surface of the fingers and toes. They are found also in the integument of other regions possessing sensibility in a high degree, such as the lips, margin of the eyelid, nipple, penis and the clitoris, as well as on the dorsum of the hand and foot, and the radial surface of the forearm. On the volar surface of the distal segments of the fingers, where they are most numerous, some twenty are found to the square millimeter. The corpuscles occupy the summit of the papillæ and ridges of the connective tissue stratum of the skin and lie close beneath the epidermis, with their long axes perpendicular. They are elongated irregular ellipsoids, often somewhat sinuous in outline, and, in the larger papillæ, two may be joined at the deeper ends to form a compound body.

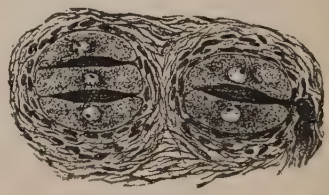


FIG. 116—Two corpuscles of Grandry from bill of duck; nerve is seen entering corpuscle on right. × 265.

The tactile corpuscles are relatively large, being from 80–150 μ long and about one third as broad. Depending upon its size, each corpuscle receives from one to four nerve-fibres, which usually enter in the neighborhood of the deeper pole and, on piercing the capsule and losing the myelin coat, divide into a number of naked axis-cylinders. These pass in parallel or spiral windings, beset with varicose thickenings, between the flattened tactile cells, the entire interlacement being embedded within a semi-fluid substance and enclosed by a thin nucleated fibrous capsule.

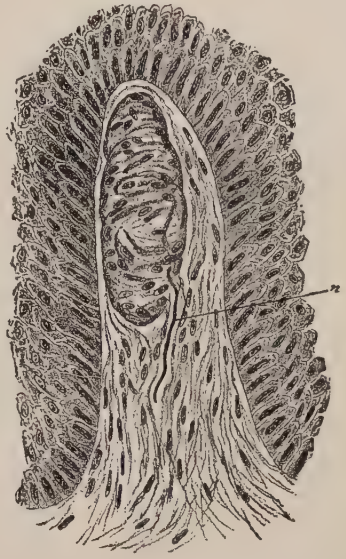


FIG. 117—Corpuscle of Meissner lying within papilla of corium of skin from finger; only deeper layers of overlying epidermis are shown; *n*, entering nerve fibre. × 270.

The End-Bulbs.—These endings include a variety of irregularly spherical or ellipsoidal bodies found in the edge of the eyelid, the conjunctiva and corneal margin, the lips and oral mucous membrane, the glans penis and clitoridis and probably other parts of the integument highly endowed with sensibility. In the conjunctiva they lie superficially placed within the connective tissue near the summit of the papillæ and folds where such elevations exist, but always close beneath the epithelium. They vary considerably in size, often being small but sometimes measuring from 50–100 μ in diameter. Usually a single nerve-fibre, exceptionally two or even more, enters each bulb, losing its myelin coat as it pierces the thin fibrous capsule. Within the latter the nerve now represented by the naked axis-cylinder, divides into from two to four branches, which, after describing several annular or spiral turns, give off varicose fibrils that divide into the terminal threads, forming an intricate maze within the semi-fluid substance (granular in preparations) enclosed by the fibrous capsule.

FIG. 118—Two end-bulbs of Krause from human conjunctiva. (*Dogiel.*)

The Genital Corpuscles.—These endings are most numerous (from one to four to the square millimeter) in the deeper strata of the corium covering the glans penis and clitoridis and occur also in the skin of the neighboring parts of the genitalia. They are of irregular oval or lobulated outline and from .02–.35 mm. in diameter. They present the same general architecture as the end-bulbs, but are larger and possess a somewhat thicker capsule and contain a more intricate interlacement of the terminal nerve-fibrillæ. The latter are

derived from the subdivision of two or three fibres that, after losing their myelin coat, enter near the base of the corpuscle. The fibrillæ are beset with varicose enlargements and club-shaped terminal swellings. The fibrous capsule consists of several connective tissue lamellæ, possessing flattened nuclei, and encloses the semi-fluid or granular substance in which the end-arborizations are embedded.

FIG. 119—Genital corpuscle from integument of penis; nerve divides before piercing capsule and terminates in intricate end-windings. (*Dogiel.*)

FIG. 120—Genital corpuscle from integument of human clitoris. × 350. (*Worthmann.*)

In contrast to the foregoing end-organs, in which the axis-cylinder subdivides into numerous terminal threads disposed as more or less elaborate intertwinings, a second group is distinguished by the presence of a **lamellated capsule** that encloses a cylindrical core, the **inner bulb,** containing the slightly branched axis-cylinder. These endings, of which the Pacinian corpuscle is representative, are relatively large and occur chiefly in the skin and the serous membranes.

A transitional form, connecting them with the spherical end-bulbs, is the **cylindrical end-bulbs.** These are found in various parts of the corium, the oral mucous membrane, and between the bundles of striped muscle and of tendon. They are irregularly cylindrical, often somewhat bent, and consist of a thin lamellated capsule that encloses a core of semi-fluid sub-

FIG. 121—Cylindrical end-bulbs attached to sensory nerves in parietal peritoneum of man. (*Dogiel.*)

stance in which is the centrally placed axis-cylinder. The latter, after losing the myelin coat on entering the proximal pole of the corpuscle, traverses the core with little or no branching until near the distal pole, where it ends in a single or slightly subdivided terminal enlargement.

The Vater-Pacinian Corpuscles.—These structures, also called the **lamellated corpuscles,** are large ellipsoidal bodies, from .5–1.5 mm. in length and about one third as much in breadth, situated within the con-

nective tissue in many parts of the body. In man they are found in the deeper layer of the corium, especially in the skin covering the palmar and plantar aspects of the fingers and toes and the nipple, in the connective tissue in the vicinity of the joints, in tendons, in the muscle-sheaths, in the periosteum, in the tunica propria of the serous membranes (the parietal peritoneum, the mesentery, and the pleura), in the neighborhood of the pancreas and of the oviduct. They are particularly large in the mesentery of the cat, where they may be detected readily with the unaided eye as oval, pearly bodies, sometimes 2–3 mm. in length.

The most conspicuous part of the Pacinian corpuscle is the robust **capsule** that contributes almost the entire bulk of the body and consists of from one to three dozen thin concentric connective tissue lamellæ. The opposed surfaces of the lamellæ are separated by a single layer of flat plate-like connective tissue cells, whose nuclei appear as fusi-form thickenings along the concentric lines mark-ing the individual lamellæ. The axis of the Pacinian corpuscle is occupied by a core of semi-fluid sub-stance, the **inner bulb,** in which the naked axis-cylin-der is embedded. On joining the proximal pole of the corpuscle, the fibrous (Henle's) sheath of the nerve-fibre blends with the lamellæ of the capsule, while the medul-lary coat is retained during the somewhat tortuous path of the fibre through the capsule as far as the core. At this point the remaining envelope of the nerve-fibre disappears, the sub-sequent part of its course, through the inner bulb being as the naked axis-cylinder. At a variable distance from, but often just before gaining, the distal pole of the core, the axis-cylinder divides into from two to four branches, each of which terminates in a slightly ex-panded end-knob. Sometimes shortly after penetrating the capsule, the nerve-fibre splits into two or more axis-cylinders, which then share in common the envelope of semi-fluid axial substance.

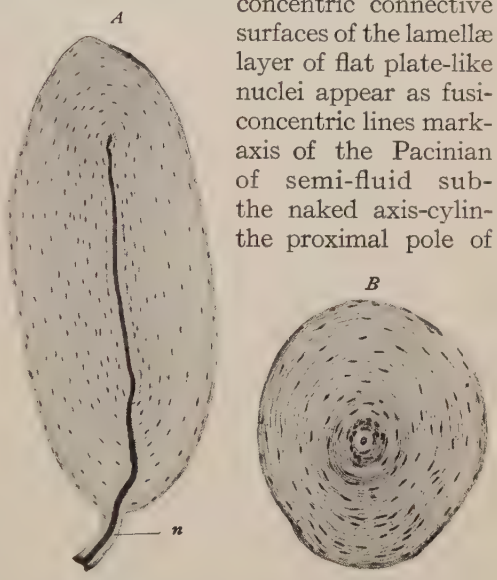


FIG. 122—Vater-Pacinian corpuscles from skin of finger; *A*, longitudinal, *B*, transverse section; *n*, nerve entering capsule to reach inner bulb. × 145.

The **Golgi-Mazzoni corpuscles,** found in the corium of the skin on the finger-bulbs and on the external genital organs, in the conjunctiva, and in the peritoneum, are modifications of the ordinary Pacinian corpuscles. They differ from the latter in being smaller and in possessing fewer lamel-læ, a relatively larger core and a more branched axis-cylinder.

Mention may be made of the **corpuscles of Herbst,** which, on account of their accessibility, are frequent objects of study. They are found in the velvety skin covering the bill and in the tongue of water-fowl and are

associated with the Grandry's corpuscles already mentioned. They closely resemble the Pacinian bodies of mammals, but differ in being smaller, relatively broader, and in exhibiting a double row of oval nuclei within the inner bulb and around the axis-cylinder.

Neuromuscular Endings.—In addition to sensory nerve-fibres which end between the muscle fibres as free terminal fibrils, voluntary muscle is provided with special sensory end-organs, long known as **muscle-spindles,** probably concerned in transmitting impulses that afford impressions as to tension, the "muscle-sense." The neuromuscular endings lie within the connective tissue surrounding bundles of voluntary muscle-fibres and are long spindle-shaped structures, varying in length from 1–5 mm. or more and in width from .1–.3 mm. where broadest. They are widely distributed, being present in probably almost all the skeletal muscles, and are especially numerous in the small muscles of the hand and foot. They have not been found in some of the muscles of the face, those of the pharynx, the intrinsic muscles of the larynx, some of the perineal muscles, and the diaphragm.

Each muscle-spindle consists of a **capsule,** composed of a few concentric layers of fibrous tissue, which encloses a group of from three to ten, but sometimes as many as

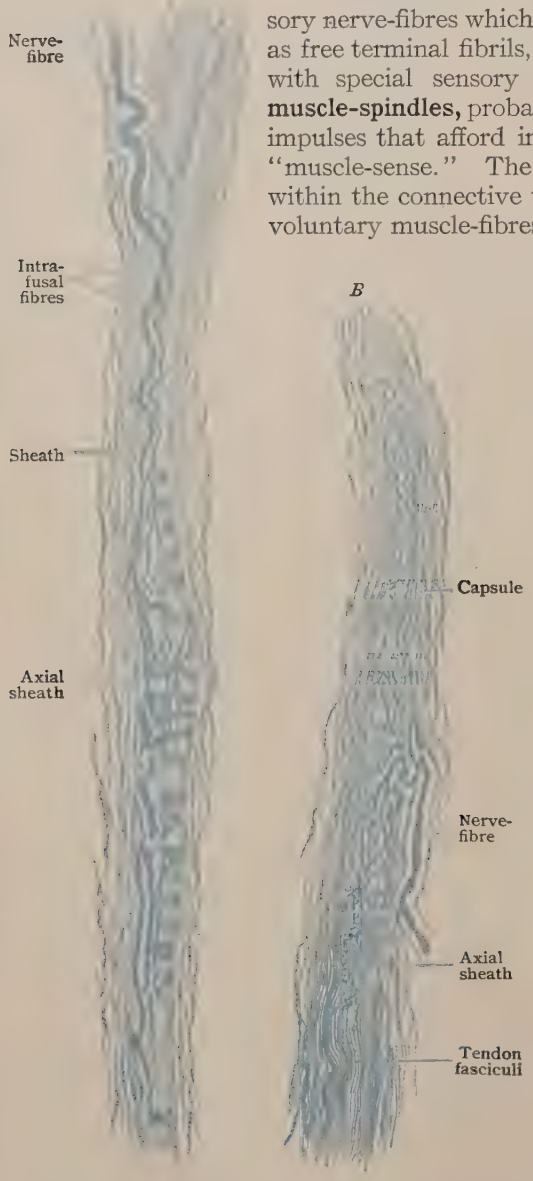


FIG. 123—*A*, neuromuscular ending; *B*, neurotendinous ending in longitudinal section, methylene blue staining. × 260. (*Drawn from preparation made by Professor Huber.*)

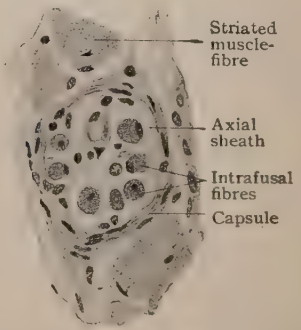


FIG. 124—Neuromuscular ending in transverse section. × 370.

twenty, striated muscle-fibres, myelinated nerves, blood-vessels, and interspersed connective tissue. These **intrafusal fibres,** as the enclosed muscle-fibres are called, differ from those of the adjacent muscle in being much smaller in diameter and length, markedly tapered toward either end, more coarsely, but less distinctly striated, and in possessing nuclei within the sarcous substance. The intrafusal fibres collectively are surrounded by a thin special fibrous envelope, the **axial sheath,** between which and the capsule lies a periaxial space. Each spindle receives usually several myelinated nerve-fibres, which, after incorporation of their fibrous sheaths with the capsule, pierce the latter at various points and proceed to the individual muscle-fibres. After repeated division during their course through the capsule and periaxial space, the nerve-fibres pierce the axial sheath, lose their myelin coat and terminate either as one or more ribbon-like branches that encircle the muscle-fibres in annular or spiral windings, or, after further subdivision as branched telodendria in which the fibrils end in irregular spherical or pyriform swellings.

Neurotendinous Endings.—In their general architecture, these end-organs resemble the muscle-spindles. They lie within the interfascicular connective tissue, at the junction of the muscle and tendon, and are probably present in all tendons, although in variable numbers. Like the neuromuscular endings, the **tendon-spindles,** as they are often called, are long fusiform structures, from 1.–1.5 mm. in length, surrounded by a fibrous **capsule.** The latter encloses a group of from eight to twenty intrafusal tendon fasciculi, which are smaller and apparently less mature than those composing the surrounding tendon-tissue. The intrafusal fasciculi are invested by a fibrous **axial sheath,** between which and the capsule lies a periaxial space. On reaching the spindle, after repeated branching, the myelinated nerve-fibres penetrate the capsule, with which their fibrous sheaths blend, and undergo further division. The myelinated coat is lost after they pierce the axial sheath, the naked axis-cylinders then breaking up into smaller fibrils that extend along the intrafusal fasciculi. The terminal ramifications, applied to the surface of the fasciculi, vary in details. Some arise as short lateral branches that partly encircle the fasciculi and end in irregular plate-like expansions, while others terminate between the smaller fasciculi. The tendon-spindles are probably concerned in appreciating the degree of tension exerted by the pull of muscular contraction.

The **terminal cylinders,** or *Ruffini's endings,* are elongated, slightly fusiform end-organs, which supplement the fine sensory nerve-endings in connective tissue. They lie at the junction of the corium and the subcutaneous layer of the fingers and toes. They resemble somewhat the tendon-spindles, being provided with a fibrous sheath which surrounds the elaborate end-arborizations of the entering nerve-fibre. The latter, sometimes single but often double, loses its fibrous sheath on penetrating the capsule with which the sheath blends, and enters the connective tissue as a naked axis-cylinder. This subdivides into numerous branches, which are beset with irregular varicosities and end in small club-shaped expansions.

Motor Nerve-Endings

The motor endings include (a) the terminations of the axones of neurones, whose cell-bodies (nerve-cells) are situated within the motor nuclei of the spinal cord and brain-stem, that pass to voluntary muscle; (b) the terminations of sympathetic neurones that end in voluntary muscle and the terminations of sympathetic neurones that end (c) in cardiac muscle and (d) in involuntary muscle.

Endings in Voluntary Muscle.—There is a double motor innervation of voluntary muscle: (1) through myelinated fibres of somatic efferent neurones whose cell-bodies are situated within the spinal cord and brain-stem, (2) through unmyelinated fibres of sympathetic efferent neurones. The former are the more conspicuous and will be described first. On approaching their peripheral destination, the myelinated efferent nerve-fibres branch repeatedly, each fibre in this way coming into relation with a number of muscle-fibres. When the myelinated

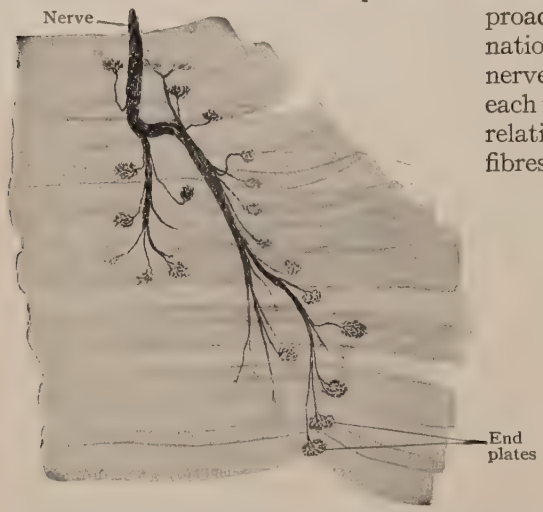


Fig. 125—Motor nerve-endings in striated muscle; bundle of nerve-fibres separates to supply the individual muscle-fibres. × 135.

Fig. 126—Motor nerve-ending in striated muscle; terminal arborization of axis cylinder lies beneath sarcolemma embedded in granular sole-plate. × 500.

nerve-fibre reaches the muscle-fibre which it supplies, its myelin coat abruptly ends and the neurilemma becomes fused with the sarcolemma, while the axis-cylinder passes beneath the sarcolemma to terminate in an **end-plate.** The latter appears as an oval field from 40–60 μ in its longest diameter, which is applied to the surface of the muscle-substance. In profile it often shows as a slight elevation. Embedded within a nucleated sheet of granular protoplasm, the **sole-plate,** lie the terminal arborizations of the axis-cylinder, formed of irregular varicosities and club-shaped ends. Usually each muscle-fibre is provided with a single motor end-plate, which may lie at an equal or unequal distance from the ends of the fibre. Exceptionally two end-plates are found on one muscle-fibre in which case the end-organs usually lie near each other. The unmyelinated fibres are numerous, but their terminations are inconspicuous. They are more diffuse than the preceding motor end-plates, and often have the form of tortuous

beaded fibres. Whether these fibres innervate all or only some of the individual muscle-fibres is still the subject of investigation.

Endings in Involuntary Muscle.—The terminations of the sympathetic axones supplying the nonstriated muscle are comparatively simple. The cell-bodies of the neurones contributing the immediate fibres of distribution to involuntary muscle of the viscera usually occupy the nodal points (microscopic ganglia) of plexuses within the walls of the organs, from which bundles of unmyelinated nerve-fibres extend to and surround the muscle-bundles. Entering the latter, the nerve-fibres divide into delicate varicose threads that pass between the muscle-cells, parallel with their long axes. As they course within the intercellular substance, the varicose fibrils give off short lateral branches that end, as does also the parent fibril, on the surface of the muscle-cells in minute terminal knobs.

FIG. 127—Motor nerve-ending in involuntary muscle. (*Huber.*)

FIG. 128—Motor nerve-ending in cardiac muscle. (*Smirnow.*)

Endings in Cardiac Muscle.—These, also the terminations of sympathetic neurones, include varicose nerve-fibrils which may be followed between the muscle-fibres. During this course side branches arise which, as well as the main fibril, terminate on the muscle-elements in endings of varying complexity. In some cases these are merely minute simple end-knobs, resembling those in involuntary muscle; in other cases they are more elaborate and of a group of secondary fibrillæ bearing nodular endings, the whole recalling somewhat the motor end-plates in striated muscle.

THE VASCULAR SYSTEM

THE vascular, or circulatory, system includes the organs immediately concerned in conveying throughout the body the fluids which bring to the tissues the nutritive substances and oxygen necessary for their metabolism and carry away from them to the excretory organs the waste products formed during metabolism.

The system is composed of two parts, the one consisting of organs in which circulates the blood, while the other consists of organs containing a colorless or white fluid known as lymph, or chyle. The former of these subsystems is the **blood-vascular system** and the latter is the **lymphatic system.** Since, however, the two systems communicate and the lymphatic system develops in close relations with the blood-vascular, it is evident that they are intimately associated both anatomically and embryologically.

THE BLOOD-VASCULAR SYSTEM

The blood-vascular system consists of (1) a system of canals known as the **blood-vessels,** traversing practically all parts of the body, and (2) of a contractile organ, the **heart**, by whose contractions the blood is forced through the vessels. The latter, in turn, are divisible into: (a) the **arteries,** which carry the blood from the heart to the tissues; (b) the **capillaries,** exceedingly fine vessels which form a network in the tissues; and (c) the **veins,** which return the blood from the tissues to the heart.

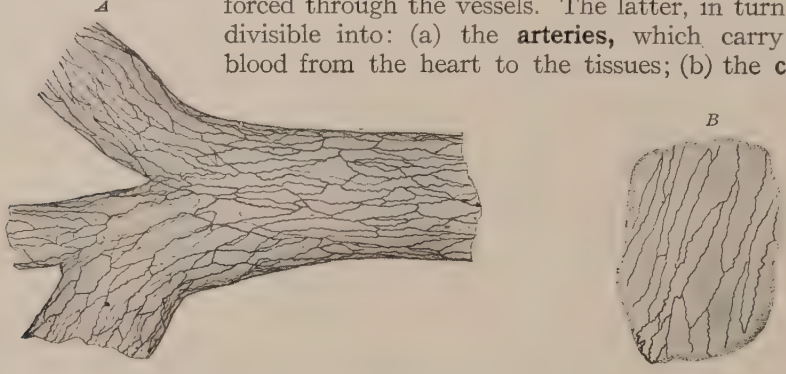


FIG. 129—*A*, endothelial lining of small artery after silver staining. × 200. *B*, endothelial cells more highly magnified. × 300.

General Structure of Blood-Vessels.—Although passing into one another insensibly and without sharp demarcation, typical arteries, capillaries, and veins present such characteristic histological pictures that they are readily distinguished. All blood-vessels, including the heart, possess an endothelial lining which constitutes the innermost layer of the **tunica intima,** or, as in the capillaries, even the entire wall of the vessel. Usually, however, the intima consists of the endothelium reinforced by a variable amount of

fibro-elastic tissue. Except within the walls of capillaries, external to the intima lies a thick middle coat, the **tunica media,** composed of intermingled lamellæ of involuntary muscle, and elastic and white fibrous connective tissue. Outside the media follows the **tunica externa,** or *adventitia*, which, although usually thinner than the middle coat, is of exceptional strength and toughness and is constructed mainly of fibro-elastic connective tissue. It should be noted that the endothelial tube is the fundamental and primary structure in all cases, the other coats being secondary and variable according to the size and character of the vessel. The customary division of the

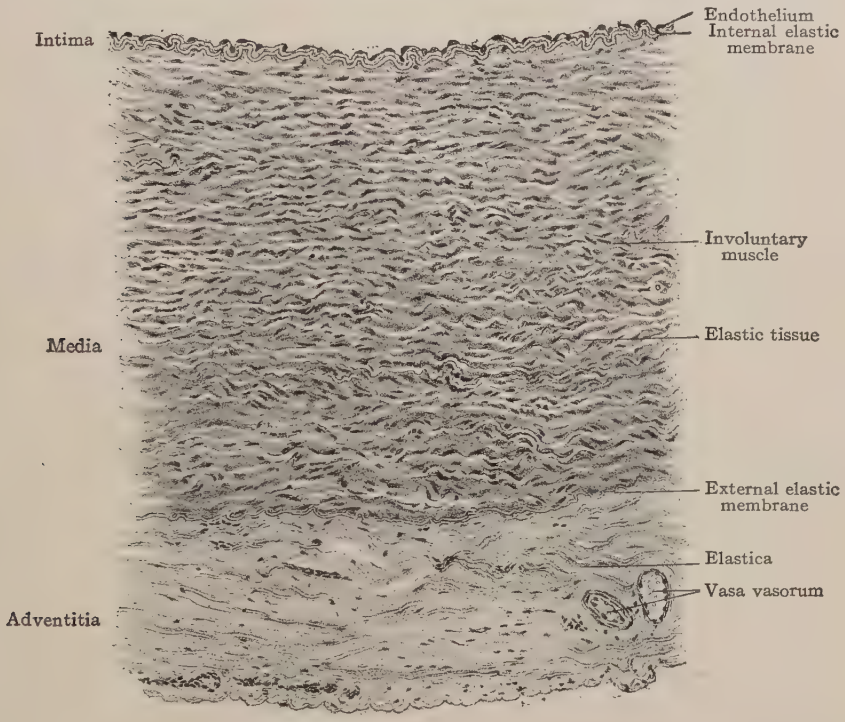


FIG. 130—Transverse section of artery of medium size.

wall into the three coats is more or less artificial and in the larger vessels often uncertain. The recognition of an inner endothelial and an outer musculo-elastic coat frequently more closely corresponds to the actual arrangement than the conventional subdivision into the three tunics.

The **endothelial lining** of the arteries consists of elongated spindle-shaped plates united by sinuous lines of cement-substance, which, after silver-staining, map out the contours of the cells with diagrammatic clearness (Fig. 129). Within the veins the endothelial plates are shorter and broader than in the arteries. The presence of small oval nuclei, not seen in silvered preparations is readily demonstrated by nuclear stains, such as hematoxylin.

The **involuntary muscle** varies in amount from the imperfect single layer of muscle-cells found in the arterioles to the robust muscular coat of many lamellæ in the larger arteries. It is relatively best developed in arteries of medium size, where the muscle occurs in distinct broad or sheet-like bundles between the strands of fibro-elastic tissue. The component fibre-cells are short and often branched and, for the most part, circularly disposed. The distribution of the muscular tissue is much less regular and constant in the veins than in the arteries, since in many veins it is scanty, in some entirely wanting, and in a few excessive, occurring as both circular and longitudinal layers. The **striated muscle** found in the large vessels communicating with the heart resembles that of the cardiac wall, with which it is continuous.

Connective tissue is represented in the arteries and veins by both fibrous and elastic tissue. The former is present usually as bundles of white fibres between the other components of the vessel-wall. The elastic tissue is conspicuous in all arteries, save the smallest, and in many veins. It presents all variations in amount from loose networks of delicate fibres in the smaller vessels to robust plates and membranes in the largest arteries. Within the intima of the latter, the elastic tissue often occurs as a sheet of closely arranged branching elastic fibres, forming the internal elastic lamina.

Nutrient blood-vessels are present in the walls of all the larger vessels, down to those of 1 mm. in diameter, and provide nourishment for the tissues composing the tubes. These **vasa vasorum,** as they are called, are usually branches from some neighboring artery; their favorite situation is the external coat, within which they break up into capillaries that, in the larger vessels, invade the media, but never the intima. The blood from the vessel-wall is collected by small veins that accompany the nutrient arteries, or, as in the case of the veins, empty directly into the venous trunk in whose walls they course.

The **lymphatics** are represented by networks of canals within the adventitia. In certain situations, conspicuously in the retina, the blood-vessels are enclosed by lymph-channels, the **perivascular lymph-sheaths,** that occupy the outer coat.

The **nerves** distributed to the walls of blood-vessels are numerous and include both efferent and afferent fibres. These form a perivascular plexus around the vessel from which motor (sympathetic) fibres pass to the involuntary muscle, while the sensory fibres end within the outer and inner tunics. Special nerve-endings have been described in both the external and internal tunics.

The Arteries.—In cross-sections of arteries of small and medium size, after the usual methods of preservation which cause some contraction of the vessels, the **intima** presents a plicated contour. The **internal elastic lamina** appears as a conspicuous corrugated light band, marking the boundary between the inner and middle tunics. The lining endothelial cells are so thin, that in profile their presence is indicated chiefly by the slightly projecting nuclei. The endothelium and the elastic membrane are separated by a thin layer of fibro-elastic tissue. The **media,** thick and conspicuous, consists

of circularly disposed bundles of involuntary muscle separated by lines of elastic tissue. After the usual stainings, these lines appear light and almost uncolored, but after selective dyes, as basic fuchsin and orcein, the elastica

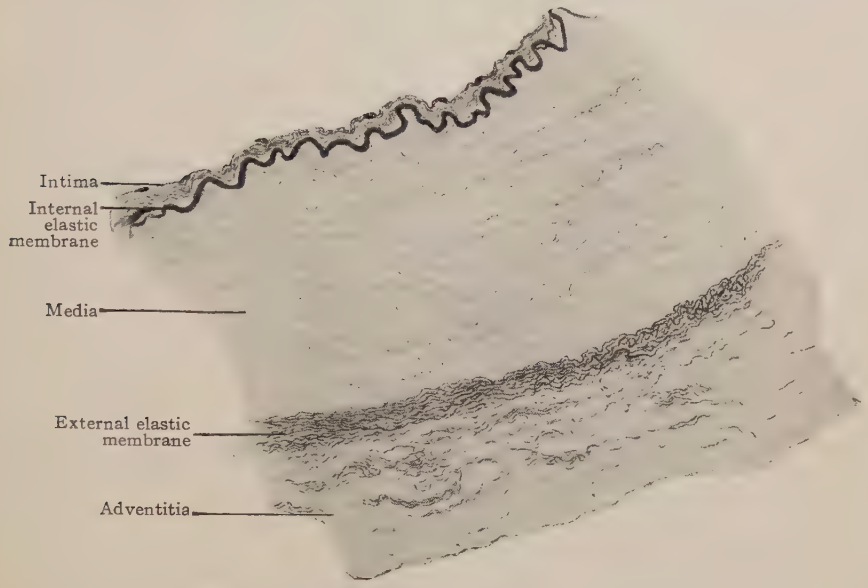


FIG. 131—Transverse section of artery of medium size, stained to show elastic tissue. × 100.

is very conspicuous (Fig. 131). Delicate bundles of fibrous tissue lie among the musculo-elastic strands. The outer boundary of the media is marked by a more or less distinct **external elastic membrane.** This is usually broader, but less condensed than the internal elastic lamina. The **adventitia** varies

FIG. 132—Small arteries, arterioles and capillaries from pia mater. × 150.

in thickness, being relatively better developed in the medium-sized arteries than in the larger ones. It consists of bundles of fibrous tissue intermingled with elastic fibres of varying thickness. Sometimes scattered bundles of longitudinal muscle are present. The adventitia contains the nutrient blood-

vessels and the chief lymph-channels and blends with the surrounding areolar tissue without sharp demarcation.

Followed towards the capillaries, the coats of the artery gradually diminish in thickness. The elastic tissue becomes progressively reduced until it entirely disappears from the middle coat, which then is a muscular tunic with a slight admixture of fibrous tissue. Before the capillary is reached, the muscle is reduced to a single layer of cells which in turn gives place to groups of muscle-cells that partially surround the vessel. After the disappearance of the muscle-cells the blood-vessel has become a true

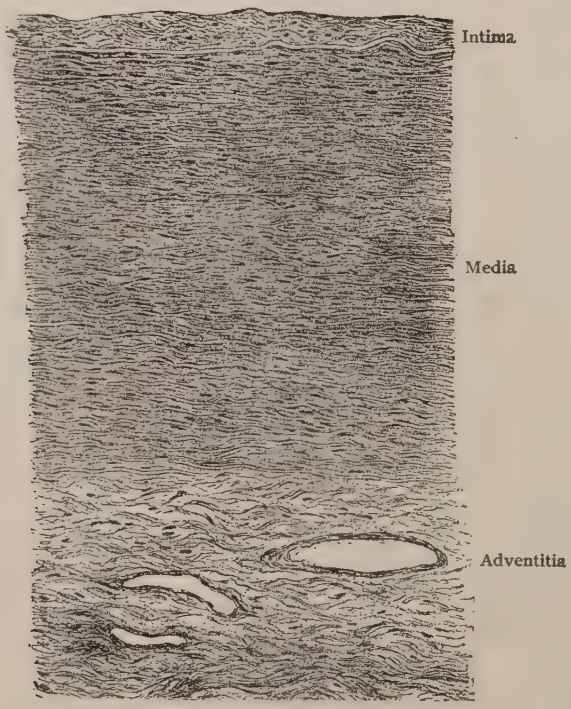


FIG. 133—Transverse section of abdominal aorta. × 90.

capillary. The adventitia shares in the general reduction, and in the smallest arteries consists of only a few fibro-elastic strands outside the scattered groups of muscle-cells.

In the **large arteries** chiefly the intima and media thicken. Although the inner coat greatly increases and contains a large amount of fibrous tissue and elastica, a conspicuous internal elastic membrane is often lacking. The character of the thickened media also changes, the muscle being relatively reduced and overshadowed by the excessive amount of fibro-elastic tissue, which confers a more compact and denser character to the wall of the vessel. The adventitia, while proportionately thinner than in arteries of medium size, is also increased, and consists of robust fibres and close networks of elastica, and strong bundles of fibrous tissue. Exceptionally scattered

bundles of involuntary muscle are found within the external tunic. In the roots of the aorta and pulmonary artery, the media consists chiefly of cardiac muscle resembling the myocardium with which it is continuous, both vessels having been derived from the anterior segment of the primary heart-tube.

The Veins.—Although the walls of the veins are thinner than those of the corresponding arteries, their thickness for veins of a given diameter is not constant, owing to the frequent irregularity in the composition of the tunics. In consequence of the smaller amount of muscular and elastic tissue that they contain, veins are generally more flaccid and less contractile than the arteries which they accompany. In veins of medium size, the **intima** consists of the lining endothelium, the cells of which are broad and short, a thin layer of fibrous tissue and networks of elastic fibres. A distinct internal

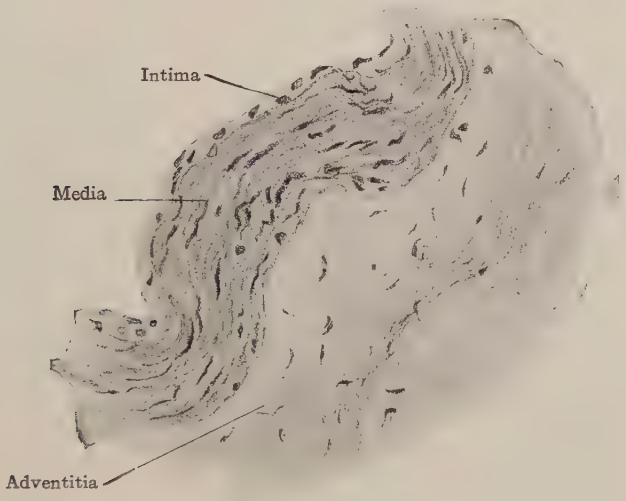


FIG. 134—Transverse section of vein of medium size. × 250.

elastic membrane is seldom present. In some veins, as the cephalic, basilic, mesenteric, iliac, femoral, and saphenous, the intima contains bundles of involuntary muscle. The **media,** the most variable coat of the vein-wall, consists of circularly-disposed, thin sheets of muscular and fibro-elastic tissue, reinforced by longitudinal strands of fibro-elastic tissue and, sometimes, muscle. In certain veins, as the saphenous, deep femoral, and popliteal, these longitudinal strands constitute a distinct zone beneath the intima. While in the larger veins the intima is only exceptionally increased, as in the hepatic portion of the inferior vena cava and the portal vein, the media is often markedly thickened. This increase is due chiefly to excess of the elastic and fibrous tissue, the muscle remaining proportionately scanty. The splenic and portal veins, however, are particularly rich in muscular tissue. On the other hand, the media may be almost wanting, as in the greater part of the inferior vena cava and the larger hepatic veins, or entirely disappear, as in the superior vena cava and in the veins of the pia and dura

mater, of the retina, and of bone. The **valves** with which many veins are provided consist of paired crescentic projections of the intima, covered on both sides with endothelium. The two layers of endothelial plates are separated by a thin stratum of delicate fibrous tissue, which contains a dense network of elastic fibres beneath the inner endothelium.

The Capillaries.—The most favorable arrangement for efficient nutrition, is manifestly, one insuring the passage of the blood-stream in intimate relations with the tissue-elements and at a reduced rate of speed. These requirements are met in the capillaries, whose collectively increased calibre and thin walls favor slowing of the blood-current and the passage of the plasma and oxygen into the surrounding tissues. The walls of the capillaries consist of endothelium only, the entire vessel being in fact a delicate endothelial tube. The cells composing the latter are elongated lanceolate

FIG. 135—Capillaries arising from arteriole and ending in small vein; from the omentum. × 150.

plates, united by narrow lines of cement-substance and containing oval nuclei. Although the transition from the arterioles is usually gradual, the final disappearance of the arterial muscle-cells marks the beginning of the true capillaries. The passage of the latter into the veins is less definite, since muscular tissue is wanting in both the capillaries and the smaller veins. In the smallest capillaries, two endothelial plates may suffice to encircle the entire lumen; in the larger three or four cells may be required to complete the vessel. The escape of leucocytes (diapedesis) and the passage of all nutrient substances as well as of minute particles of foreign substances such as dyes in the colloidal condition, take place through and between the endothelial plates. When capillaries course in dense fibrous tissues, not uncommonly the vessel is accompanied by ensheathing delicate strands of connective tissue, the **adventitia capillaris.**

In certain organs, conspicuously in the liver, the ultimate blood-vessels arise by the invasion and subdivision of the larger primary blood-channel

by the developing tissue-cords. Such blood-vessels are known as **sinusoids** (Minot) and differ from ordinary capillaries in connecting entering, afferent, and emerging, efferent, vessels of the same nature, both being always venous in character. Capillaries, on the contrary, establish communication between arteries and veins. In consequence of the invagination and intergrowth which takes place between the original blood-channel and the tissue of the developing organ, the endothelium of the sinusoids has an unusually intimate relation to the cords of tissue-cells, little or no connective tissue intervening.

The **capillaries** are arranged usually as networks, the component channels of which are of fairly constant diameter within a particular tissue. During life, it is probable that none are too small to permit the passage of the red blood-cells while many admit two or even three such elements abreast. Their usual diameter varies between 8 and 20 μ. The capillary networks in various parts of the body differ in the form and closeness of their meshes, since these details are influenced by the arrangement of the elements and by the function of the structures supplied. Thus, in muscles, tendons, and nerves the meshes are elongated and narrow; in glands, lungs, and adipose tissue they are irregularly polygonal; in the liver-lobules they converge; while in the subepithelial papillæ of the skin and mucous membranes the capillaries commonly form loops. In general, the greater the functional activity of an organ, the closer is its capillary network. Organs actively engaged in excretion, as the kidneys, or in the elimination of substances from the blood, as the lungs and liver, as well as organs producing substances directly entering the circulation, organs of internal secretion, as the thyroid gland, are provided with exceptionally rich and close networks.

THE BLOOD

The blood represents the product of the activities of many organs and consists of a clear, almost colorless **plasma,** or **liquor sanguinis,** in which are suspended vast numbers of small free protoplasmic elements, the **blood-corpuscles.** The latter are of three chief kinds—the colored cells, or **erythrocytes,** the colorless cells, or **leucocytes,** and the minute cytoplasmic bodies, the **platelets,** or **thrombocytes.** The characteristic appearance of the blood is due to the presence of hemoglobin contained within the erythrocytes which, while individually only faintly tinted, collectively impart the familiar hue, as well as a certain degree of opacity. That the characteristic pigment is limited to the cells is shown by the lack of color and transparency of the plasma when examined under the microscope, although to the unaided eye the blood appears uniformly red and somewhat opaque.

The Colored Blood-Cells.—As usually seen, the mature colored blood-cells, **erythrocytes,** or **red corpuscles,** of man and other mammals (except those of the camel family, which are elliptical in outline) are small biconcave circular non-nucleated disks, with smooth contour and rounded edges. Because they lack nuclei they are not complete cells, and for this reason some prefer to call them **erythroplastids.** During all their

developmental stages, however, they possess nuclei, and it is not until they are about to enter the general circulation that the nuclei disappear. Vertebrates below mammals have nucleated erythrocytes throughout life. When viewed by transmitted light, the individual "red" cells of mammals possess a pale greenish-yellow tint and only when they are collected in masses or in several layers is the distinctive blood-color evident. The peculiar form of the corpuscle as ordinarily seen—biconcave in the centre and biconvex at the margin—renders accurate focussing of all parts of its surface at one time impossible, the cell appearing according to focal adjustment, either as a dark ring enclosing a light centre, or *vice versa*. Viewed in profile, the disk presents a figure somewhat resembling a dumb-bell, the thicker margins of the cell being connected by the thinner concave centre. The biconcave discoidal form of the mammalian erythrocytes is the one ordinarily exhibited during life, but this is readily altered into a cup-shape by various environmental conditions, such as traversing a capillary of smaller diameter than the disk, or of being suspended in a fluid having an osmotic pressure less than that of normal plasma (Arey, '17). The fact that cup-shaped forms are seen in sections of fixed tissues is attributed to the action of the preserving fluids.

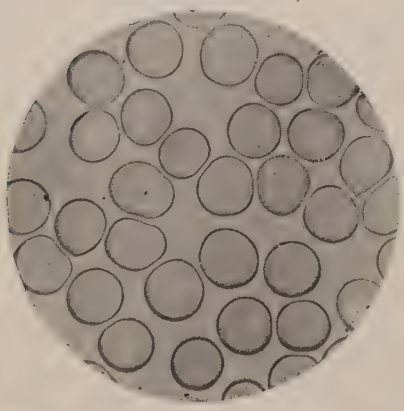


FIG. 136—Human colored blood-cells, spread into a single layer and dried. × 1000.

The structure of the red blood-cell has long been and still is a subject of dispute. According to one view the cell consists of a soft pliable envelope enclosing a fluid contents containing the coloring matter, the hemoglobin. The other view regards the corpuscle as composed of an extremely delicate spongy stroma, containing the hemoglobin, but without a distinct investing membrane. It seems probable that although no definite envelope is present in the sense of a distinct cell-wall, a peripheral condensation of the semi-fluid and hemoglobin-containing stroma exists (Jolly, '23; Cupp, '15).

The average diameter of the discoidal red blood-cells of man is 7.8 μ, some corpuscles measuring as little as 4.5 μ and others as much as 9.5 μ. Their thickness is about 1.8 μ. The average diameter of the cup-shaped corpuscles is 7 μ and their thickness 4 μ. It is probable that the average size is uninfluenced by sex and is constant for all races. The number of red cells contained in one cubic millimeter of normal human blood is approximately 5,000,000 in the male and something less (4,500,000) in the female. As individuals, they have a short life in the circulation, probably about one month, so that new ones are constantly being formed to take the place of those disappearing. The above numbers, therefore, represent the resultant of a nicely balanced adjustment between cell-formation and cell-destruction,

which is readily changed in many physiological as well as pathological conditions. The numbers of corpuscles is practically the same whether the blood be taken from the arteries, capillaries, or veins, but is lower in the blood from the lower extremity than from the upper, owing to the larger proportion of plasma in the more dependent parts of the body. In general, the red blood-cells of mammals are small and their size, which greatly varies in different orders, bears no relation to that of the animal. The corpuscles of man are among the largest and exceeded by only those of the elephant (9.4 μ) and of the two-toed sloth. The human cells are approximated in size by those of some small mammals—guinea-pig (7.5 μ), dog (7.3 μ), rabbit (6.9 μ) and cat (6.5 μ). Those of many familiar animals, as the horse, hog, sheep and goat, are distinctly smaller. The smallest corpuscles (2.5 μ) are those of the musk-deer. The positive recognition of human blood, as differentiated from that of some of the domestic animals, by measurement of the red cells, is uncertain and often impossible. The non-nucleated mature red cells are the distinguishing characteristic of mammalian blood, the red cells of the other vertebrates being nucleated and, with few exceptions, large oval elements. The largest red cells are found in the tailed amphibians; those of the amphiuma are the largest known and attain the gigantic length of 80 μ.

FIG. 137—Human blood-corpuscles; two leucocytes are seen among the red cells, most of which are grouped in rouleaux. × 625.

After fresh blood has been distributed as a thin fluid layer, the red cells soon exhibit a tendency to become arranged in winding rows, with their broad surfaces in contact, similar to piles, or **rouleaux**, of coin. The erythrocytes are very sensitive to reagents and other environmental conditions and readily undergo change and distortion. Exposure to even a current of air often produces conspicuous effects. Alterations in form result from the action of solutions of lower or higher density than that of the normal plasma. The latter is conveniently substituted by an isotonic (0.9 %) solution of sodium chloride. If the proportion of salt be reduced, the corpuscles swell, at first losing their concavity, then assuming the spherical form, parting with their hemoglobin, and becoming colorless. When subjected to hypertonic saline solutions the exterior of the corpuscles becomes irregular and beset with knob-like projections and the corpuscles are said to be **crenated**; increased concentration of the solution leads to marked shrinkage and distortion, until the cells lose all resemblance to their usual form. Certain reagents, as water, aqueous dilutions of acetic acid, and ether, promptly decolorize the erythrocytes by extraction of the hemoglobin. The hemoglobin passes out into the plasma, leaving the corpuscles as faint shadows. This is the process of **laking** of blood, or **hemolysis.** Dilute acid solutions soon completely destroy

the red cells, but leave the colorless cells intact. This fact is made use of when one wishes to count the colorless cells alone. When the fresh blood is diluted with 2 per cent. acetic acid, the red cells disappear, leaving the colorless cells in plain view.

The Colorless Blood-Cells.—When examined in fresh and unstained preparations, the colorless cells, or leucocytes, appear as pale nucleated elements which, by their pearly tint and refracting property, are readily distinguished from the much more numerous erythrocytes. Their shape is variable, but when first withdrawn from the body is usually irregularly spherical or oval. When placed on a warmed slide and maintained at the temperature of the body, the colorless cells exhibit amœboid motion, whereby not only alterations in their outlines but also changes in their actual position are produced. Although always present, the nucleus may be obscured by the overlying cytoplasm; it is most distinct when the cell is expanded as when undergoing amœboid changes. The size of the colorless corpuscles varies with the type of the cell, as described below, but in general their diameter is larger than that of the erythrocytes, being commonly from 10–12 μ. Their number is much less than that of the red cells, the usual ratio being about one colorless to six hundred red cells. Even within physiological limits this ratio varies considerably, from 5000 to 10,000, with an average of 7500, white cells being normally found in one cubic millimeter of human blood.

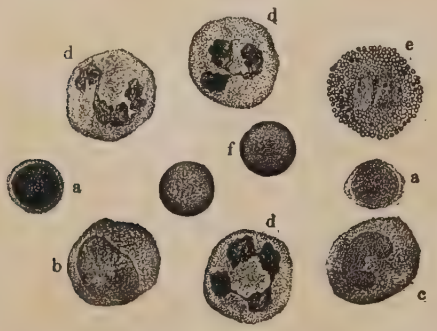
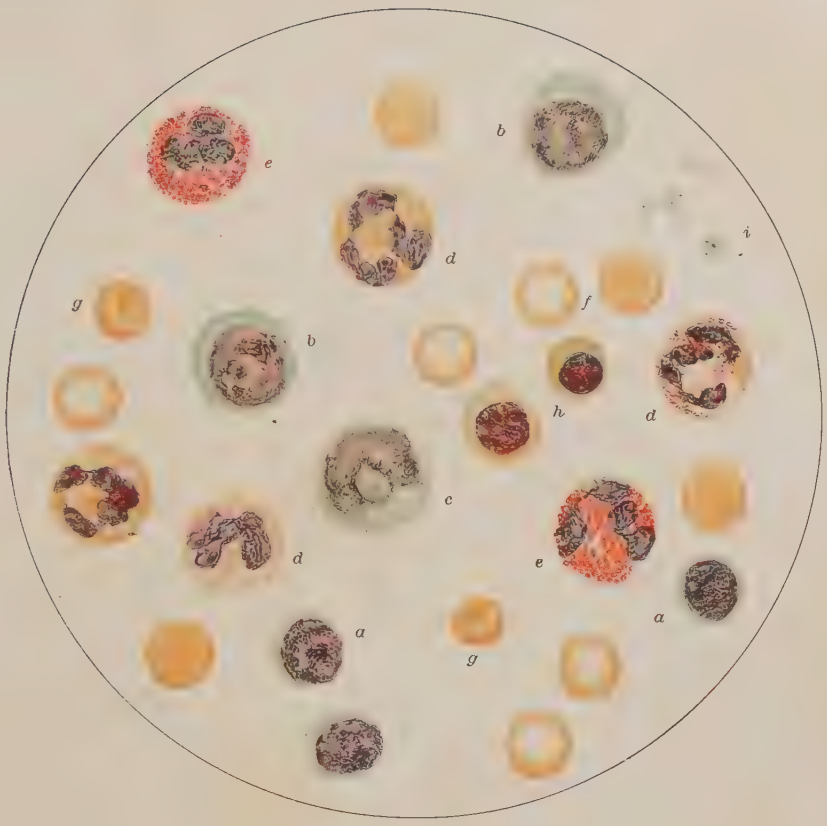


FIG. 138—Varieties of blood-cells seen in normal human blood; *a*, lymphocytes; *b*, *c*, monocytes; *d*, neutrophilic granulocyte; *e*, acidophilic granulocyte; *f*, erythrocytes. × 900.

For diagnostic purposes, the white blood-cells are studied usually in films or smears, which have been stained by a special blood-stain such as Wright's, or Jenner's, or by Jenner-Giemsa. The films or smears are made by touching a clean cover glass with a drop of blood following a puncture of the skin. A second clean cover glass is placed upon the first, and when the film has spread out evenly, the two cover glasses are slid apart. In a successful preparation there will be an evenly-spread, thin film of blood on both cover glasses. If the cover glasses are not perfectly clean, or if the blood has begun to clot the result is not satisfactory. After staining (see colored plate), three types of colorless cells may be distinguished in normal blood. These are (1) **granulocytes,** (2) **lymphocytes,** and (3) **monocytes.** Each type has definite morphologic and staining characteristics by which it may be recognized.

Granulocytes, or leucocytes with specific granules in their cytoplasm, comprise three varieties which are differentiated especially by the staining affinities of their granules. The first variety is stained characteristically by neutral dyes, the second by acid dyes and the third by basic dyes. The granules are, therefore, termed **neutrophilic, acidophilic,** and **basophilic,** respec-



HUMAN BLOOD-CELLS.

a & b, LYMPHOCYTES
c, MONOCYTE
d, NEUTROPHILIC GRANULOCYTES
e, ACIDOPHILIC GRANULOCYTES (EOSINOPHILES)
f, ERYTHROCYTES
g, ERYTHROCYTES, CUP-FORM
h, ERYTHROBLASTS
i, BLOOD PLATELETS

X 1200

SELECTED CELLS FROM PLATE IN DR. J. C. WILSON'S MEDICAL DIAGNOSIS.

tively. The three varieties of granular leucocytes are, then, (1) neutrophilic, (2) acidophilic, and (3) basophilic granulocytes. Of these three the first are usually more numerous and conspicuous, and by reason of the striking irregularities in shape of their nuclei, are commonly called **polymorphonuclears,** or **polymorphonuclear neutrophiles.**

Neutrophilic granulocytes, or **polymorphonuclear leucocytes,** are somewhat larger than erythrocytes, measuring 9–12 μ. They are usually round in smears, but when alive show active changes in shape during their amœboid movements. When observed in whole blood on the warm stage at 37° C., their average rate of locomotion is 34.1 μ per minute (McCutcheon, '23). The nucleus has typically a very characteristic, highly irregular form. Usually it is segmented, the number of segments varying from two to five. These segments are always connected by a thinner band of nuclear material. In normal blood 90 per cent. or more have the segmented form of nucleus, but in a small number the nuclei may be polymorphous, but unsegmented. In these the nucleus is usually deeply indented, often of a crescentic or horse-shoe shape. The cytosome consists of hyaloplasm in which are numerous fine granules, stainable only with neutral dyes. The color of the granules, as seen in smears after staining, varies upon the dye used. With Wright's blood stain they appear pale violet, while with Jenner's stain they appear a little more red, approaching the color of the acidophile granules, but they are always readily distinguishable from the latter by reason of their smaller size. In tissue sections, the routine hematoxylin and eosin staining does not color them differentially. These cells are by far the most common variety of colorless cells in normal blood, constituting about 70 per cent.

Acidophile granulocytes, or **eosinophiles,** have the same general morphology as the preceding, but are easily distinguished from them. The nucleus differs from that of the neutrophile in having usually but two segments. The granules in the cytoplasm differ in being larger and stainable only with acid dyes. The acid dye most frequently used in blood stains is eosin, hence the name **eosinophile.** In fresh films the granules appear large, round, highly refractile and of uniform size. In spreading the films, the cells are often broken and the granules appear scattered, but they still retain their specific staining affinities. In tissue-sections, the granules are usually preserved and stain a conspicuous red color after hematoxylin and eosin, so that acidophile cells are readily seen and recognized.

Basophilic granulocytes are present in normal blood in such small numbers that they are not always to be found. The nucleus is polymorphous, but less segmented than in the preceding varieties. It stains usually rather palely, and hence is less conspicuous than the deeply-staining basophilic granules. These vary somewhat in size, but are usually of about the same size as acidophile granules.

Lymphocytes are so called because, before entering the blood-stream, many of them have been in the lymph-vascular system, and practically all have originated in lymphoid tissues. The lymphocytes are, typically, the smallest of the white blood-cells, and are of about the same size as the

erythrocytes. They form 20 to 30 per cent. of all the white blood-cells. The lymphocytes are characterized by the fact that the nucleus is surrounded by only a thin film of cytoplasm. In addition to these typical lymphocytes, of small size, there are seen larger lymphocytes, in which the cytoplasm forms a relatively larger portion of the whole cell. But as there is no fundamental distinction either as to age or function, it is not necessary to subdivide the group of normal lymphocytes. The nucleus is the most distinct portion of the lymphocyte. In it, the chromatin is arranged in clumps or little blocks, scattered irregularly through the karyoplasm. Sometimes they form a line just within the nuclear membrane. There are frequently one or more clear spaces in the nucleus, which are usually considered as nucleoli. From the massing of the chromatin, the nucleus usually appears more darkly-stained than that of other types. The staining of the cytoplasm is decidedly basophilic. The substance responsible for this basophilic staining is diffused throughout the hyaloplasm, but is frequently less abundant near the nucleus, thus giving a peri-nuclear zone of hyaloplasm, which appears paler than the rest of the cytoplasm. The cytoplasm does not contain conspicuous granules. However, when examined with the oil immersion lens, after preparation with stains containing the dye **azure,** a few red-stained granules are seen. From their staining properties, they are termed azure, or **azurophile,** granules. Their function and origin are unknown at the present time. With vital dyes, Janus Green and Brilliant Cresyl Blue, mitochondria appear in little clumps at one side of the eccentric nucleus which in the living condition is usually not round, but slightly indented.

The **monocytes,** or **large mononuclear leucocytes,** are the largest cells of normal blood. Each has a single round or indented nucleus with a characteristic structure and a large amount of cytoplasm. The nuclei are usually larger than those of the other types of blood-cells, and in shape may be round, oval, or reniform, but are never segmented. The chromatin is evenly distributed throughout the nucleus as a fine network without the large chromatin clumps which are conspicuous in the lymphocytes. As a result the nuclei stain more palely than those of the lymphocytes. There are no nucleoli. These nuclear characters are important in distinguishing a monocyte from a lymphocyte. The cytoplasm is abundant and may retain amœboid processes after fixation. It has a homogeneous greyish color throughout.

Monocytes are usually regarded as non-granular cells, but as in lymphocytes certain azurophile granules may be distinguished in their cytoplasm after suitable preparation, and when examined with an oil immersion lens. They are smaller and more numerous than those in the lymphocytes, and contain oxydase ferments, which are lacking in the lymphocytes. If the preparations are not carefully made these granules may simulate neutrophilic granules and the cell may be mistaken for a neutrophilic granulocyte with an indented nucleus.

It is generally agreed that under the term "monocyte" are assembled cells of several origins, which are difficult to distinguish. By the supravital technic two varieties are recognized, and by other technics, three. Some pre-

fer to call them endothelial leucocytes, or endotheliocytes. The term monocyte includes the large mononuclears and transitionals of Ehrlich. Until the results of the different methods of study of this group of cells have been correlated, it is best to use the inclusive term monocyte.

Platelets, or Thrombocytes.—The blood of man and of other mammals contains constantly small non-nucleated bodies, the blood-platelets. Because they lack nuclei, some prefer to call them **thromboplastids.** They are circular, sharply-outlined disks, having a diameter of two to three microns. In the centre of each are a few highly refractile granules, which are azurophilic in their staining properties. In adult man the platelets average 200,000 to 300,000 per cubic millimeter of blood, but the number varies greatly in different conditions of the body. When brought into contact with any foreign surface, they lose their form and take part in the production of fibrin threads. They thus play an important part in the clotting of the blood. As blood issues from a wound, the contact of the platelets with the cut tissues brings about fibrin formation, and a clot is gradually formed which narrows the opening of the wound and so obstructs the hemorrhage. Because of their rôle in the mechanics of coagulation of the blood, they are also called thrombocytes. Like erythrocytes, they are non-nucleated structures in mammals, but are nucleated in the vertebrates below mammals. When coagulation is observed under the microscope it will be seen that the strands of fibrin form a network, with the platelets at the intersections of the strands. In blood films, made in the usual manner, the tendency of the platelets to clump together is shown by the fact that they are usually found in groups, although scattered single ones are also to be seen. In order to prevent clumping, the blood may be drawn directly into a drop of 1 per cent. osmic acid or into a drop of Toisson's fluid placed upon the skin. By puncturing the skin through the fluid, the blood immediately mingles with the preservative fluid and an even distribution is insured. This method is necessary in making accurate counts (Cramer, *et al.*, '23). Platelets are formed by the fragmentation of the cytoplasmic processes of the bone-marrow giant cells, or **megakaryocytes** (Wright, '10).

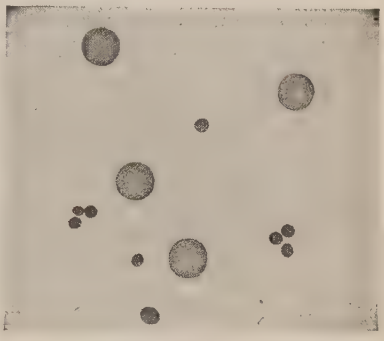


FIG. 139—Human blood, showing erythrocytes and blood-platelets × 625.

Blood-Crystals.—The most important constituent of the red cells, the hemoglobin, exists within the stroma of the corpuscles as a complex but loose, chemical combination of iron with a globulin. The hemoglobin must be freed by solution before crystallization occurs. After liberation, or "laking," as it is called, as by the addition of a weak solution of ammonium oxalate, the coloring matter of the blood, in the form of oxyhemoglobin, separates as microscopic crystals. The investigations of Reichert and Brown ('09) have shown that the forms of these blood-crystals bear a constant and

definite relation to genus and species, so that differentiation between many animals is possible, since the crystals of the species of any genus belong to the same crystallographic system and generally to the same crystallographic group. The crystals derived from the blood of man are elongated rhombohedra; from the horse, rhombic plates; from the guinea pig, tetrahedra; and from the squirrel, hexagons. On mixing dried blood with a few grains of sodium chloride, and a small quantity of glacial acetic acid, and heating until bubbles appear, minute brown crystals are formed in large numbers. These are **hemin crystals** and derived from the reduction of hemoglobin. They indicate only the presence of blood and are valueless in differentiating the blood of man from that of other animals. In blood-clots of long standing, minute crystals of hematoidin often appear as yellowish-red plates. This substance is likewise a reduction-product of hemoglobin, and is seemingly identical with bilirubin of the bile.

After death or upon standing after withdrawal from the body blood undergoes coagulation, whereby the corpuscles become entangled among the innumerable delicate filaments of **fibrin.** In microscopical preparations of fresh blood, the fibrin appears after a time within the plasma in the form of innumerable delicate threads, which cross and interlace in all directions and radiate from centres marked by groups of blood-platelets. The entanglement of the corpuscles in the fibrin-net results in the production of a dark red, jelly-like mass, the **blood-clot** or *crassamentum,* that separates from the surrounding clear straw-colored fluid, the **serum.**

DEVELOPMENT OF THE BLOOD-VASCULAR TISSUES

The Blood-Vessels.—The earliest blood-vessels within the embryo are networks of delicate channels within the mesoderm. The large vessels of the trunk arise by consolidation and fusion of the axial portions of the network; the extension of the smaller vessels occurs by the growth and conversion of the angioblastic cells with which the primary blood-tubes are intimately connected. The development of new vessels proceeds from the cells constituting the walls of the preëxisting channels. These walls consist of delicate endothelial plates from which pointed sprouts grow into the surrounding tissue. These outgrowths are at first solid, but later become hollowed out by the gradual extension of the lumen of the parent vessel. All vessels consist at first of a single layer of endothelial cells. This simplicity persists in the capillaries, while the walls of the larger vessels become reinforced by additional layers differentiated from the surrounding mesodermic tissue.

Formation of Blood-Cells, or Hemopoiesis.—The cells seen in the blood are contributed by many different organs, of which the bone-marrow and lymphoid organs are the chief ones in postnatal life. In the former are produced the erythrocytes, granulocytes, thrombocytes, and part of the monocytes. In the latter are formed the lymphocytes and some of the monocytes.

All blood-cells are formed in tissues, which have been derived from

mesoderm, and in all the blood-forming organs mentioned above there is a certain type of cell differentiated from mesenchymal cells, which is regarded as the type from which most of the cells of the blood are derived. This is known as the **hemocytoblast**, or **hemoblast,** and, as seen in sections prepared by special methods (see Technic), is distinguished by the intensely basophilic staining of the cytosome, which however contains no granules except a few mitochondria. These cells are usually, but not always, large. The nuclei are round, and occupy the greater part of the cell. The chromatin is arranged as small punctate particles evenly distributed throughout the nucleus, giving a very fine-meshed network appearance. In contrast to the deep blue staining cytosome, the nucleus has a relatively pale appearance. Several nucleoli are present, varying from two to six. The recognition of this type of cell is important for from it are developed in the several sites

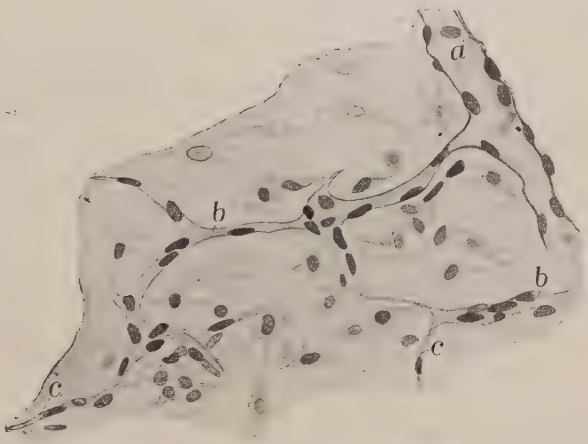


FIG. 140—Developing blood-vessels in embryonal subcutaneous tissue; *a*, large capillary; *b*, young capillaries; *c*, solid protoplasmic outgrowths forming new vessels. × 300.

of blood-cell formation most of the cells seen in the circulating blood. In abnormal conditions affecting the blood-forming organs, immature cells of one or more varieties are released into the blood-stream, and the recognition of them in smears serves as a valuable aid in diagnosis and prognosis.

Development of Erythrocytes.—Although the normal erythrocytes of the circulating blood contain no nuclei, they all have nuclei as they develop within the bone-marrow. It is only just before they are released into the blood-stream that their nuclei disappear. If they are released into the circulation precociously, they still show their nuclei and by reason of this are easily detected in the blood-films. The developmental stages of red blood-cells which contain nuclei are called **erythroblasts.** In their later stages, usually called **normoblasts,** the nuclei are small, round, deeply-staining bodies, in which the chromatin is densely packed and nearly homogeneous. Their cytosomes are characterized by the presence of hemoglobin, which is strongly acidophilic. As the normoblasts are derived through a series of generations from the hemoblasts, it is possible to recognize two

intervening stages of development, (1) **proerythroblasts,** and (2) **polychromatophilic erythroblasts.** The proerythroblasts, like the parent hemoblasts, have strongly basophilic cytoplasm, due to the presence of a homogeneous basophilic substance, and do not show the presence of hemoglobin. The nucleus is large in relation to the size of the cell, and is round or slightly oval. The chromatin is arranged in little particles giving to the nucleus a granular appearance. Later the chromatin granules begin to show radial arrangements. Nucleoli are present in the earliest forms, but may be absent later. The **polychromatophilic erythroblasts** represent the next phase following that of the proerythroblasts. Hemoglobin has begun to appear, at first in small amount, but gradually increasing. Concurrently, the basophilic substance is diminishing. The mingling of the acidophilic hemoglobin with the basophilic substance gives rise, in stained preparations, to various shades of purple. These several shades of color seen in the same cytosome constitute **polychromatophilia.** If the basophilic substance is aggregated into minute scattered granules, this is called **basophilic stippling.** The nucleus is gradually decreasing in size, and as the chromatin particles become more closely massed the staining increases in intensity. The radial arrangement of the chromatin is often well marked, and there are no nucleoli. The succeeding stage is one most readily recognized and, is characterized by the presence of hemoglobin in the cytosome, and by having a small, round, compact, deeply-staining nucleus. This is often called the normal orthochromatic erythroblast, or **normoblast.** It is present in small numbers in the circulation of the newborn child, but soon disappears.

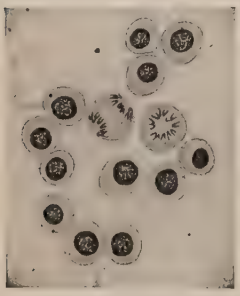


FIG. 141—Embryonal blood; dividing erythroblasts. × 600.

The final phase in the life-history of the erythroblast before it becomes an erythrocyte is the loss of the nucleus. The manner in which the nucleus is lost is either by extrusion as a whole, or by fragmentation and absorption. It is possible that both these processes occur. Sometimes a very small nuclear mass remains, appearing as a dark-staining round body in an otherwise mature erythrocyte. These particles, often less than one micron in diameter, were observed independently by Howell and Jolly, and so are termed Howell-Jolly bodies. Another nuclear remnant appears in the form of a ring, which is probably the remains of the nuclear membrane, after the chromatin has disappeared. In form, it may be round, or figure of eight, or even more irregular. As it was first described by Cabot, it is usually called Cabot's ring. When present, it is often associated with other signs of immaturity of the cell, as polychromatophilia. Erythroblasts, particularly in the early stages of their development, divide by mitosis. These are seen normally in sections of bone-marrow, but only in blood-films when a pathological condition is present.

In addition to the normal erythroblasts, or normoblasts, which are found in normal postnatal bone-marrow, there are **embryonal erythroblasts,** or **megaloblasts,** which occur in the early fetal sites of blood-formation,

before blood-formation begins in the liver, and also appear in the circulation at that time. These are mentioned here because, although they do not probably occur normally in the adult, they appear in the circulation in pathological conditions. In development they pass through stages similar to that of the normal erythroblast and these stages are correspondingly named,—promegaloblast, polychromatophilic megaloblast, and orthochromatic megaloblast.

During the early embryonic development, megaloblasts are derived from the lining endothelium of blood-vessels, and in the adult experimental animals, under highly pathological conditions, this mode of formation of red blood-cells has also been observed. To what extent this method occurs in normal postnatal life is still the subject of active investigation.

Development of Granulocytes.—The granular leucocytes pass through a definitely recognizable period of development, in which they are known

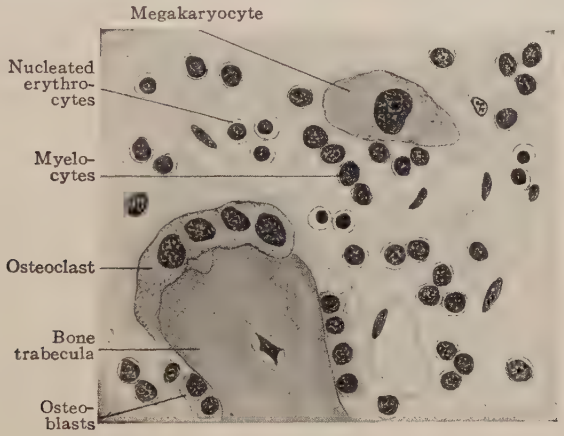


FIG. 142—Section of embryonal bone-marrow, showing nucleated erythrocytes, myelocytes and megakaryocyte. × 625.

as **granuloblasts** or, to use an older but less distinctive term, **myelocytes.** In normal postnatal life, these cells are found only in the red bone-marrow, but in diseases of the blood-forming organs, they are released prematurely into the circulation. They are cells with round nuclei, but have already distinctive specific granules in the cytosome. These granules may be neutrophilic, acidophilic, or basophilic, according to which variety of granulocyte, each granuloblast, or myelocyte, will become when mature. Since the granuloblast is derived from an earlier non-granular cell with a round nucleus, the hemocytoblast, and develops further into a granular leucocyte with an irregular nucleus, there are a number of intermediate stages distinguishable. The identification of these stages depends upon seeing especially the variations in the number of granules in the cytosome, and the degree of indentation of the nucleus. The stage between the typical granuloblast as described above and the mature granulocyte is characterized by having the nucleus single, but distinctly indented and is termed the **metagranuloblast,** or **metamyelocyte.**

The stage between the typical granuloblast and the hemoblast is that of the **progranuloblast**, or **promyelocyte.** This has the nucleus rounded, and the cytosome shows granules and also some of the basophilic substance derived from the hemoblast. The younger the stage, the less easy it is to distinguish it from the hemoblast and early stages of lymphoblasts. When the specific granules are first beginning to form they do not have their differential staining characters, but all stain alike. They stain purple-violet with the methylene-azur component of Wright's stain, and hence are azurophilic at this stage. These granules already contain oxydase ferments. This very early stage of a promyelocyte is sometimes termed the **myeloblast,** or unripe **granuloblast.**

Development of Lymphocytes.—Lymphocytes undergo fewer changes in their cytomorphosis than do most of the other cells of the blood. Immature lymphocytes or lymphoblasts are characterized by the nuclear chromatin being arranged in small particles, so that the nucleus has a smooth, even appearance. In the older and mature stages, the chromatin becomes arranged in large flakes. The cytoplasm is basophilic throughout their life-history. Because of the relatively slight changes seen in the various stages of development, it is often difficult or impossible to identify the age of developing lymphocytes.

Development of Monocytes.—The cells, assembled under the term monocyte are a heterogeneous group, and have different origins. Some arise from the primitive blood-cells, the hemocytoblasts in the bone-marrow and others from the reticulo-endothelial system of the spleen, lymph-nodes, liver, and bone-marrow. Immature monocytes, the so-called monoblasts, are not easily identified.

Development of Megakaryocytes and Formation of Platelets.—The megakaryocytes are the largest cells of the bone-marrow engaged in producing blood-elements. They are derived by growth and differentiation from the hemocytoblasts. The younger stages are smaller, with a single nucleus, which is round or slightly lobulated. The size of the cell increases with its age. In the younger forms the cytoplasm is basophilic, without granules, but soon granules appear in the peripheral part of the cytosome, and increase until they are seen in all parts, These granules are **azurophilic,** and have the same staining properties as those in the platelets. The megakaryocytes continue to grow until they reach a very large size, and the nuclei assume various lobulated forms. These larger cells, as studied by J. H. Wright ('10), were seen to lie alongside small blood-vessels, and the pseudopodial extensions of their cytoplasm to penetrate the vessel-wall, and to project within the lumen. From the tips of these pseudopodia small fragments are evidently detached and immediately carried away in the circulation, as blood-platelets. The formation of platelets, according to these observations, is due to the breaking up of the cytoplasm of the megakaryocytes which have reached a certain stage of growth and development, and when once begun in any one cell is probably rapidly completed, after which the nucleus degenerates. It takes place in various ways but usually by the pinching off of single, small, rounded projections, or pseudopods, or by the segmentation of longer, slender

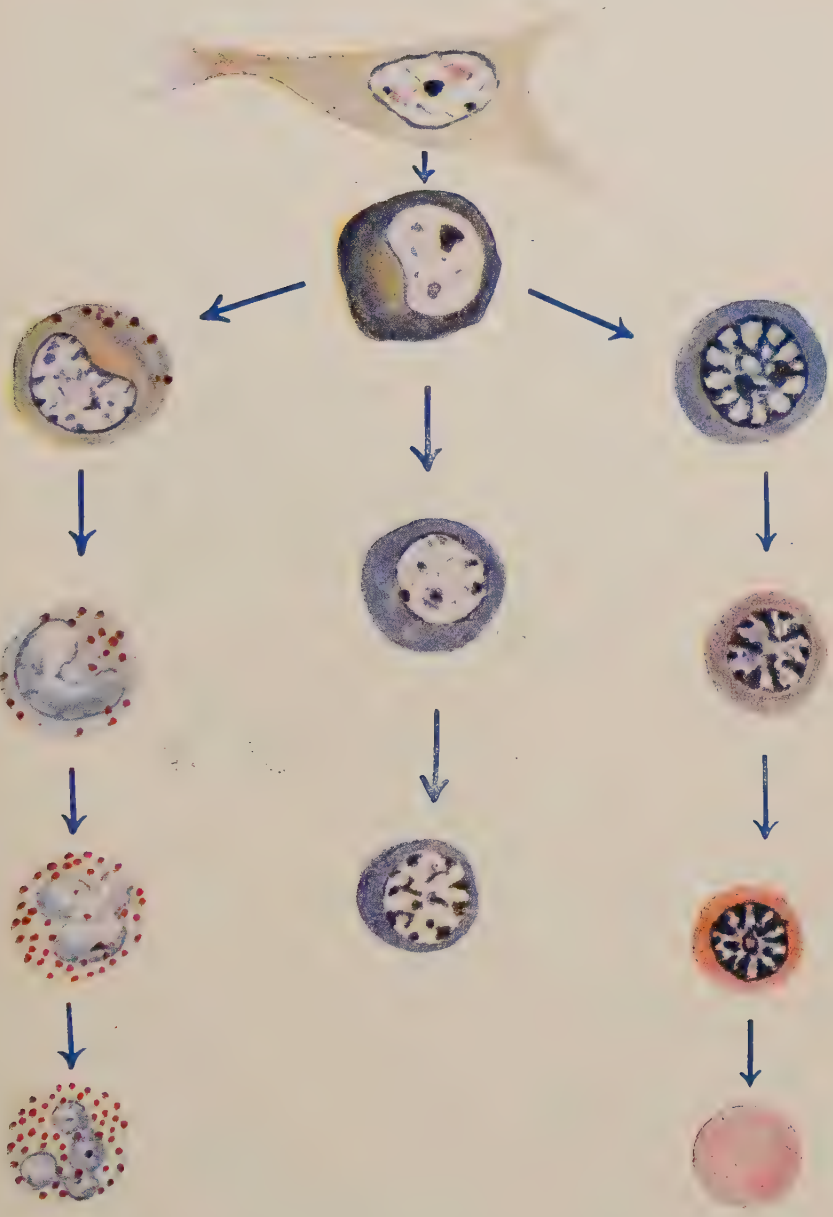


FIG. 143.—Diagram of blood formation; developmental stages of granulocytes, lymphocytes and erythrocytes.

pseudopods. Before the separation of the platelet takes place, the azurophilic granules in that portion of the cytoplasm which is to form the platelet become aggregated into a little group, surrounded by a zone of hyaline cytoplasm. The lines of cleavage are through this zone of hyaline cytoplasm, and the little group of granules becomes the central granular mass of the platelet which has been regarded by some observers as a nucleus.

THE HEART

In principle, the heart is a modified blood-vessel, formed by the fusion of two heart-tubes and converted into an efficient organ for propulsion by the unusual development of muscular tissue within its walls. As are the walls of the larger arteries, so also is that of the heart composed of three general layers. The inner of these, the **endocardium,** consists of an endothelial lining and the fibro-elastic tissue. The middle layer, the **myocardium,** contributes

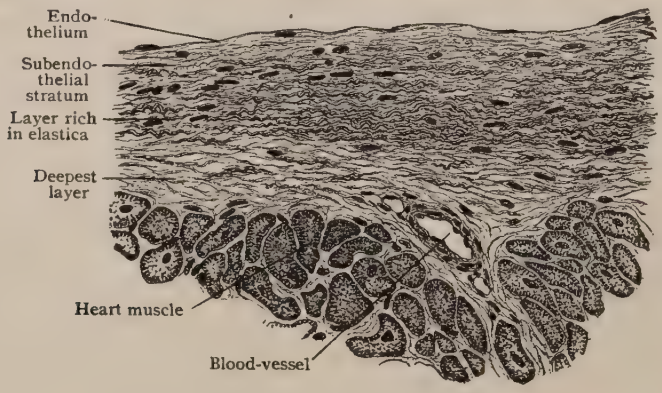


FIG. 144—Section of endocardium. × 325.

by far the greatest bulk of heart-tissue and is made up of intricately arranged sheets of cardiac muscle and fibro-elastic tissue. The outer layer, the **epicardium,** the visceral layer of the pericardium, is a stratum of fibro-elastic tissue, covered externally, except at the base where the great vessels join the heart, with mesothelium.

The Endocardium.—The endocardium follows all the irregularities of the interior of the heart, lining every recess and covering the free surfaces of the valves, tendinous cords, and papillary muscles. It consists of a single layer of endothelial plates and the underlying connective tissue. The latter contains many scattered strands of fibrous tissue and is rich in elastic fibres. The elastic tissue occupies particularly the deeper parts of the endocardium, being almost wanting beneath the endothelium, and in the auricles, or atria, where it is most abundant, it may be condensed into fenestrated membranes. The deepest layer of the endocardium blends with the connective tissue of the subjacent myocardium.

The **valves** of the heart are essentially duplicatures of the endocardium, strenghtened in their thicker parts by fibro-elastic tissue. In the case of the

auriculo-, or **atrio-ventricular valves,** this tissue is continuous with the dense fibrous rings (annuli fibrosi) to which the leaflets are attached. Towards the free margin of the valve, the layers are blended and reduced to a thin fibrous stratum covered on both sides by endothelium. Strands of nonstriated muscle occur near their attached borders, while the fibro-elastic tissue of the chorda tendineæ is continuous with the middle layer. The **semilunar valves,** guarding the aorta and the pulmonary artery, correspond in their

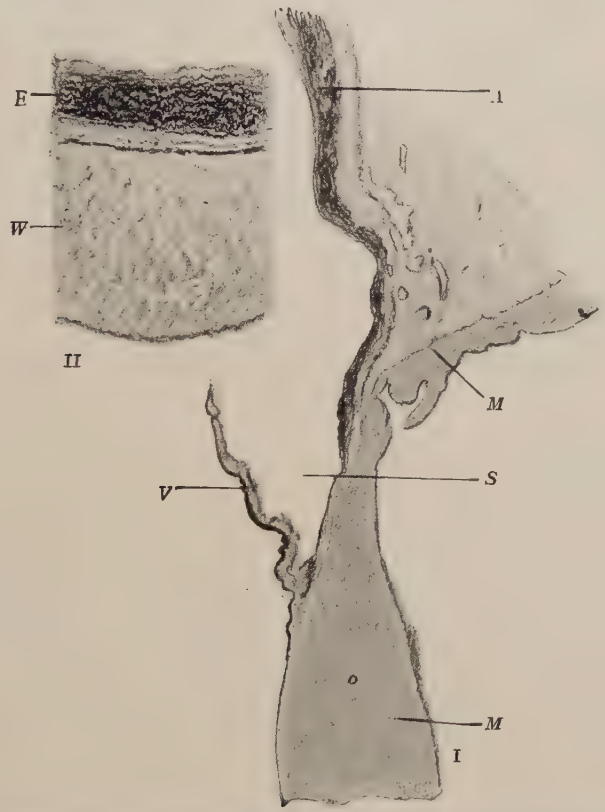


FIG. 145—I, Longitudinal section of human heart with aorta: A, aorta; M, heart muscle: S, sinus of valsalva; V, aortic valve leaflet. × 5; II, Aortic valve; E, elastic tissue; W, white fibrous connective tissue. × 90.

general structure with the other valves, although the muscle in them is wanting. At the periphery and in the central thickenings, or **noduli,** of the leaflets, the elastic tissue is particularly rich. Within the folds guarding the orifices of the interior vena cava and of the coronary sinus, the interendothelial connective tissue is an inconsiderable layer, which, in the case of the Eustachian valve, is sometimes further reduced by absorption resulting in a fenestrated condition of the leaflet.

The Myocardium.—The middle layer of the heart-wall, the myocardium, is composed of a close elongated network of muscle-fibres, the intermuscular spaces of which are filled with connective tissue. The

latter corresponds to an endomysium and, within the ventricles, contains only a small amount of elastic tissue, except around the openings of the valves. In these locations, dense plates of fibrous tissue (annuli fibrosi) encircle the valvular orifices and contain many elastic fibres, as well as give attachment to the strands of cardiac muscle. Although as ordinarily seen in microscopical preparations, the fibro-muscular sheets that compose the myocardium seem to follow no particular arrangement, it has been shown that in the architecture of the heart they are disposed according to a definite but complex plan.

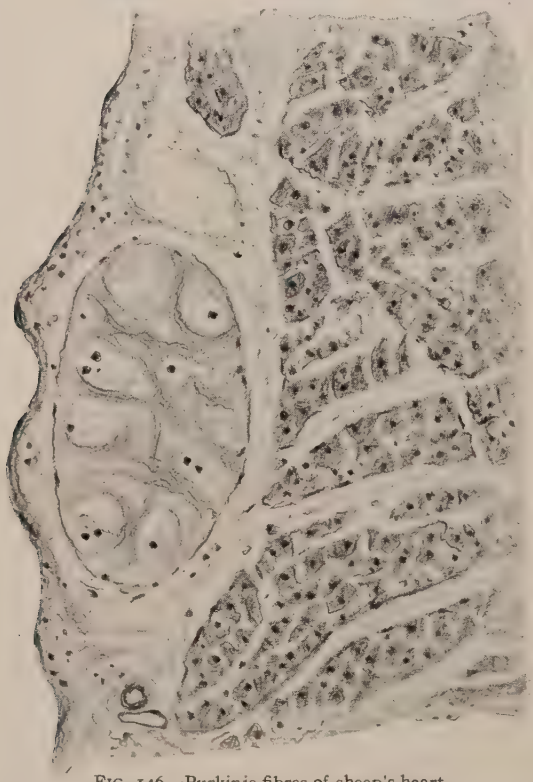


FIG. 146—Purkinje fibres of sheep's heart.

In addition to the ordinary fibres of cardiac muscle, the subendocardial layer of the myocardium in many places, especially in the ventricles, contains peculiar fibres, distinguished by their large size, pale color, and abundant sarcoplasm, with a corresponding lessening in the number of contractile fibrillæ. These have long been known as **Purkinje fibres,** but their significance has only recently been recognized. They are now regarded as the terminal part of an elaborate system of special muscle-fibres whose probable function is the coördinative connection of the atrial and ventricular musculature, that otherwise are distinct and unconnected. The most evident part of this system is the definite **atrio-ventricular bundle,** which, beginning in the atrial wall in the vicinity of the coronary sinus, passes from the interatrial septum, under the attachment of the posterior valve, into the pars membranacea septi; here dividing into a right and left limb, the bundle continues into the interventricular partition. Although distinct and compact during this course, at its two ends the atrio-ventricular bundle breaks up into radiating and interlacing strands, which form an intricate network composed of Purkinje fibres. The latter disappear among the elements of the myocardium. The Purkinje fibres ramify not only within the septum between the heart-chambers, but also invade the trabeculae (columnæ carneæ) and papillary muscles of the ventricles. For a time muscular throughout their length, the papillary

muscles become transformed into the fibrous chordæ tendineæ in the segments attached to the valves. These fibrous cords often contain considerable elastic tissue which is continuous with the fibro-elastic layer of the valve-leaflets.

The Epicardium.—The external layer of the heart-wall, the epicardium, corresponds in its general structure with other parts of the pericardium. It consists, as do other serous membranes, of a single layer of mesothelial cells that covers the free surface of the heart and rests upon a stratum of fibro-elastic connective tissue. The elastic fibres are very fine and numerous and form a dense network immediately beneath the endothelium. Those within the atrial epicardium are prolonged into the adventitia of the great veins, while the elastic fibres of the ventricular covering end before reaching the aorta and pulmonary artery. Where not separated from the muscle by subserous fat, which may be abundantly present even in normal hearts, especially in the atrio-ventricular and the interventricular grooves, the epicardium is intimately attached to the subjacent muscular coat. The numerous branches of the coronary vessels, as well as the nerve-trunks and the microscopic ganglia connected with the coronary plexuses, lie beneath the epicardium or within its deepest layer.

Blood-Vessels.—The unusually generous vascular supply of the heart includes the branches derived from the **coronary arteries** and the capillaries. The former ramify beneath the epicardium and are, to some extent, *end-arteries*, that is, arteries which do not directly anastomose with their neighbors. Although both the epicardium and the deepest layer of the endocardium contain small vessels destined for their tissues, it is to the heart-muscle that the blood is chiefly directed. The larger vessels of the myocardium course within the more robust tracts of connective tissue, giving off the twigs which resolve into the capillary networks. These exhibit elongated meshes, similar to those seen in voluntary muscle, which enclose the muscle-fibres. The relation of the capillaries to the individual fibres is most intimate, since in many places the capillaries are received in grooves, or almost tunnels, in the muscle-substance. The valves are devoid of blood-vessels, with the exception of those accompanying muscular tissue within the bases of the auriculo-ventricular leaflets.

The **lymphatics** of the heart are arranged in two sets, a network within the deepest layer of the endocardium and a network beneath or within the epicardium. These networks communicate with the larger lymphatic vessels which lie in the atrio-ventricular groove.

The **nerves** are many and contributed by the vagus and the sympathetic. They include both myelinated and unmyelinated fibres which form the coronary and many small subsidiary plexuses. Scattered in these superficial plexuses lie numerous nerve-cells, sometimes singly but often collected into microscopic ganglia. They are especially plentiful around the orifices of the great veins opening into the atria, a vicinity corresponding to the upper end of the atrio-ventricular bundles, and over the upper parts of the ventricles. Nerve-fibres and ganglion-cells have been demonstrated within the atrio-ventricular bundle. The distribution-twigs contain both efferent

(motor) and afferent (sensory) fibres. The immediate motor fibres supplying the heart-muscle whose axis-cylinders end on the surface of the muscle-fibres, usually in minute swellings, are probably exclusively the axones of sympathetic neurones, since it is doubtful whether the vagus fibres extend beyond the cell-bodies of such neurones, which they enclose in terminal arborizations. The sensory fibres, at least in part from the vagus, are distributed to the epicardium, endocardium, and the connective tissue of the myocardium. Within the epicardium especially, and to a limited degree also in the other layers, the afferent fibres are connected with endings which resemble the neurotendinous spindles.

The Pericardium.—The parietal pericardium corresponds in its general structure to that of the visceral portion, the epicardium, above described. Its free surface is covered with a single layer of mesothelial plates, which rest on the connective tissue layer. The latter consists of fairly dense fibrous tissue, intermingled with fine elastic fibres, which form a close network immediately beneath the mesothelium. Where not intimately attached to the pleura, a much looser **subserous layer** of fibro-elastic connective tissue is present. This, as well as the outer part of the pericardium, contains a variable amount of adipose tissue. The **blood-vessels** and **nerves** of the pericardium are comparatively few; some of the nerves, which are chiefly afferent, are connected with Pacinian corpuscles. The **lymphatics** are represented by definite channels within the connective tissue. The lymphatics beneath the mesothelium possess thin walls and stand in intimate relation to the pericardial sac. Particles pass between the endothelial plates into the lymph-channels although no preformed openings, or stomata, exist.

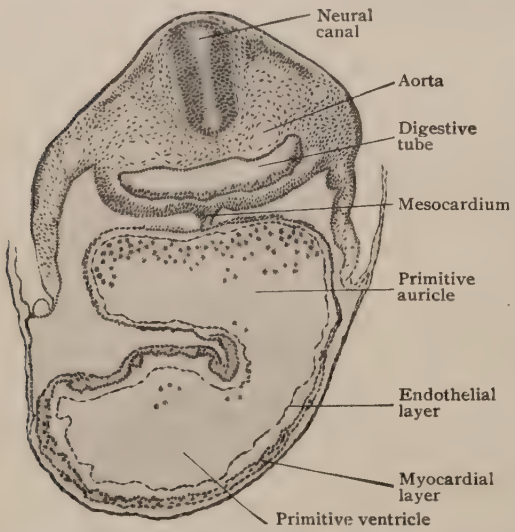


FIG. 147.—Transverse section of early rabbit embryo passing through young heart, showing venous segment behind and arterial in front. × 75.

Development of the Heart.—A systematic account of the formation of the heart is beyond the purpose of these pages. Suffice it to note, that, very early in the young embryo, two heart-tubes are folded off in the visceral layer of the mesoderm. These tubes, at first entirely separate, gradually approach the ventral mid-line and eventually fuse, a single heart thereby arising. The wall of the latter, as well as of the primary tubes, consists of two layers separated by a distinct space. The inner of these layers is composed of a single strand of very delicate mesodermic elements, which become

the lining of the heart; it is, therefore, known as the **endothelial heart** and lies within the outer **myocardial layer** of the heart-wall as a shrunken cast within a mould. The outer layer is, from the first, thicker and exhibits a tendency to form trabeculæ, the resulting myocardium being for a time loose and spongy. Later, the two layers of the heart-wall come into contact, when the endothelial stratum becomes applied to the irregular surface of the myocardium, every ridge and pocket of which receives an investment of endothelium. The subsequent consolidation which the heart-walls undergo brings about the effacement of the primary spongy texture of the myocardium, except within the innermost zone, where the ridges and bands of the columnæ carneæ remain throughout life as the manifestations of the primary condition. During these changes, the mesenchyma of the trabeculæ differentiates into the syncytium from which arise the myofibrils of the later heart-muscle and into the connective tissue filling the interstices between the networks of muscle-fibres. The structural peculiarities of the cardiac fibres, as contrasted with those of ordinary striated muscles, indicate a less complete differentiation in the heart-muscle, this being particularly true of the Purkinje fibres. These characteristics are probably correlated with the exceptional activity that the heart-muscle is called upon to endure, since, as seen in the "red" muscles, a lower degree of histological differentiation favors prolonged exertion, although at the expense of rapidity of contraction. The valves are formed from cushion-like thickenings of the mesenchyma. Those surrounding the primary efferent vessel, the truncus arteriosus, lead to the subdivision of this tube into the aorta and the pulmonary artery and, likewise, to the formation of the three leaflets of the semilunar valves. In the case of the auriculo-ventricular valves, the septal leaflets are formed from the endocardial cushions, which appear on the surfaces of the partition, septum intermedium, that divides the auricular canal, the channel connecting the primary auricular and ventricular segments of the heart. The other leaflets of these valves are derived from the walls of the auricular canal, a process of undermining partially freeing portions of the innermost layer of the heart-wall. These overhanging plates are connected, however, with the ventricular myocardium by strands of tissue, the later papillary muscles, which for a time are entirely muscular. Eventually the muscle-tissue disappears near the valve-leaflet and the bands are converted into the fibrous strands, the chordæ tendineæ.

THE LYMPHATIC SYSTEM

The lymphatic, or lymph-vascular, system consists of an almost universally present system of channels which are definite tubes, the **lymphatic vessels.** The vessels contain the **lymph,** a fluid usually colorless and containing numerous corpuscles, the **lymphocytes.** Since the latter are familiar as one of the chief types of colorless blood-cells, they are described in connection with the blood in which they circulate. Although the lymph is ordinarily clear, that within the lymphatics leading from the intestines

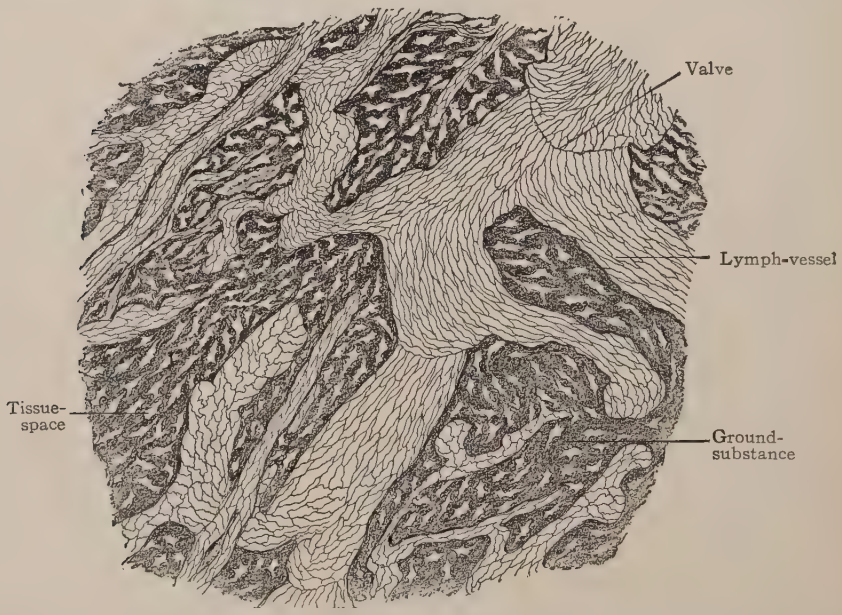


FIG. 148—Portion of central tendon of rabbit's diaphragm, treated with silver nitrate; lymphatic vessels are shown as light irregular tracts; tissue spaces are seen within dark ground-substance. × 120.

appears, especially during digestion more or less milky, in consequence of the presence of numerous globules of fat which have been taken up from the intestinal contents. For this reason these intestinal lymphatics are often termed **lacteals.** The lymphatics resemble the veins in the walls of which, indeed, they originate, and into which they finally pour their contents. They arise from capillaries, have walls closely resembling in structure those of the veins and are provided with many valves. The lymphatics form a system which is closed, except where the two chief trunks open into the subclavian veins, the capillaries beginning as networks or blind channels. The most striking feature of the lymph-paths, however, is the presence along the vessels of more or less conspicuous masses of lymphoid tissue, the **lymph-nodes.**

Tissue-Spaces.—These spaces exist practically in all structures of the body, for the most part, however, as the interfascicular clefts within connective tissue. The tissue-spaces are filled by a clear watery fluid, the tissue-fluids, and are sometimes imperfectly lined by flattened connective tissue cells. The spaces present great variations in size. They come into intimate relation with the lymphatic capillaries, but do not actually open into the latter. In most localities, the spaces and lymphatic capillaries are separated by only delicate partitions which allow the passage of fluids, and also of wandering cells, from the tissue-spaces into the lymph-vessels and *vice versa*.

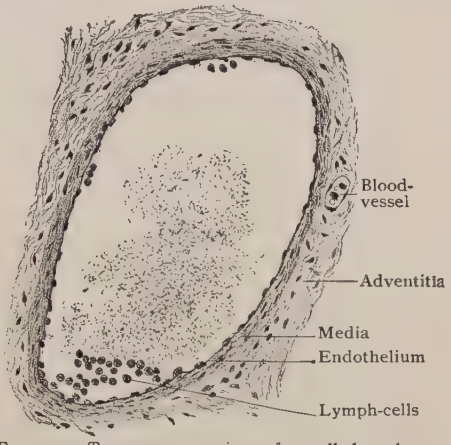


FIG. 149—Transverse section of small lymph-vessel. × 160.

The Lymph-Vessels. — The definite lymph-paths include the **capillaries** and the **vessels.** The lymphatic capillaries are arranged in **networks,** varying in closeness and complexity, and resemble in structure the blood-capillaries, consisting of a single layer of endothelial plates. They differ from the blood-capillaries in being usually much greater in calibre and less regular in size (30–60 μ), larger and smaller capillaries, often beset with irregular constrictions and enlargements, being indefinitely interspersed.

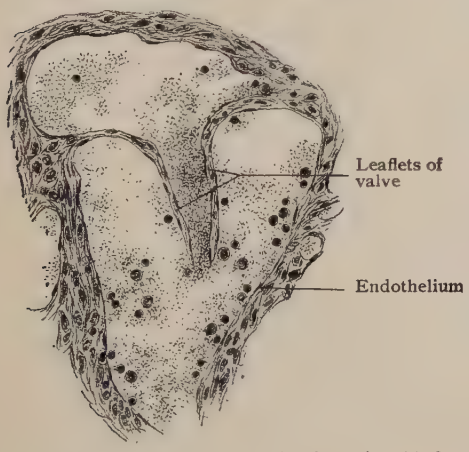


FIG. 150—Section of lymphatic, showing valve. × 180.

The larger lymph-channels, the **lymphatics,** as they are commonly called, which arise from the networks of lymph-capillaries and convey the lymph ultimately to the subclavian veins, closely resemble the veins in arrangement and structure. The larger lymph-vessels (from .5 mm. and upwards) possess walls consisting of three coats, which are much like those of the veins. These include: (a) the **intima,** composed of the endothelial lining and a thin layer of fibro-elastic tissue; (b) the **media,** made up of circular involuntary muscle interspersed with connective tissue and few elastic fibres; and (c) the **adventitia,** consisting of fibro-elastic tissue and, sometimes, of longitudinal bundles of smooth muscle. The numerous **valves** are essentially folds of the intima. In tissue-sections, the lymphatics are often distinguishable from small veins by the character of

their contents. No red blood-cells are seen within normal lymphatic vessels, but are usually present in veins. Indeed, the lymphatics appear nearly empty, except for small numbers of nucleated cells and a fine granular precipitate, the latter the result of the fixing fluid upon the lymph-plasma.

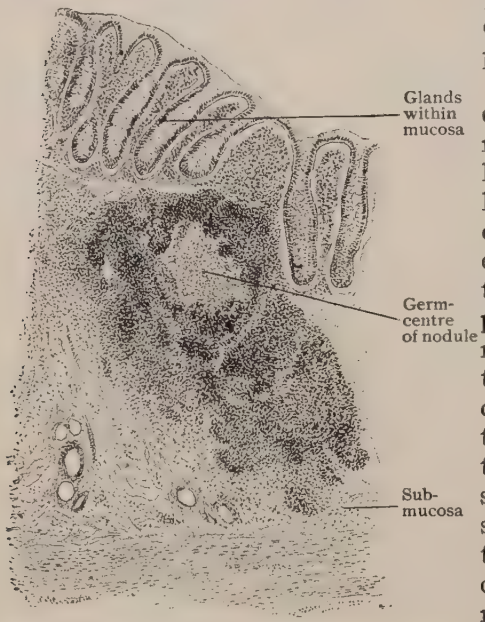


FIG. 151—Simple lymph-nodule from large intestine. × 120.

Lymphoid Tissue.—Wherever found, whether as diffuse masses, simple nodules, or as the larger and complex lymph-nodes, lymphoid, or adenoid, tissue is composed of two chief constituents—the supporting connective tissue **reticulum,** and the **lymphoid cells** contained within the meshes of the reticulum. The latter varies in the number of the component cells and fibres and the size of its meshes, but in the denser types of lymphoid tissue, as in the periphery of the solitary nodules and in the cortical follicles and medullary cords of the lymph-nodes, it is so masked by the innumerable overlying cells that only after removal of the latter can the supporting framework be satisfactorily demonstrated. The reticulum is a form of connective tissue, which is included in the reticulo-endothelial system, because its cells are, to a certain extent, phagocytic. Where of exceptional delicacy, the reticulum is formed almost entirely by the anastomosing processes of the stellate connective tissue cells, but usually there are present, in connection with the cells, thin bundles of fine fibres. The lymphoid cells are exceedingly numerous and closely packed and present the characteristics of the lymphocytes in the blood, this resemblance being explained by the fact that such blood-cells are derived from the lymphoid tissues.

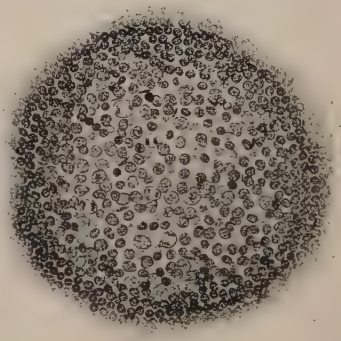


FIG. 152—Portion of lymph-nodule showing details of germ-centre. × 280.

The **simple lymph-nodules,** varying in size but seldom more than 2 mm. in diameter, are irregularly spherical or ellipsoidal masses of lymphoid tissue, in which a denser peripheral zone encloses and blends with a less compact core. Within the latter, which being of looser texture appears as

a lighter central area, usually are seen lymphoid cells in various stages of mitotic division. Such foci are known as **germ-centres** and indicate the birthplaces of many new lymphocytes. Definite lymph-channels are found neither upon the surface of, nor within, the simple nodules; the latter are provided, however, with a generous network of capillary blood-vessels. Intermediate in complexity between the simple nodules on the one hand and the typical lymph-nodes, on the other, stand such structures as Peyer's patches and the faucial tonsils, in which groups of simple nodules are blended into a single organ, the component nodules only partially retaining their individuality.

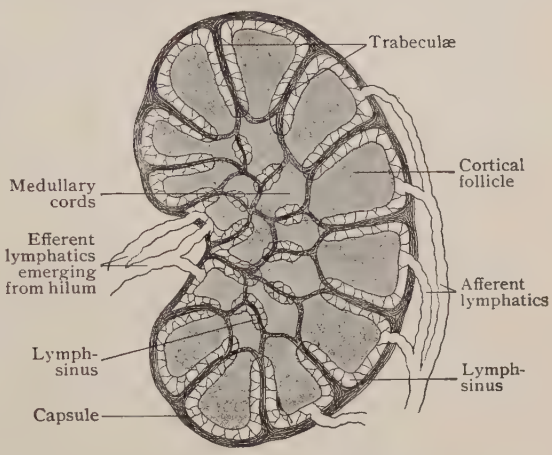


FIG. 153—Diagram illustrating architecture of lymph-node.

The **lymph-nodes** are flattened oval or bean-shaped bodies, from a few millimeters to two centimeters or over in length, that are scattered along the

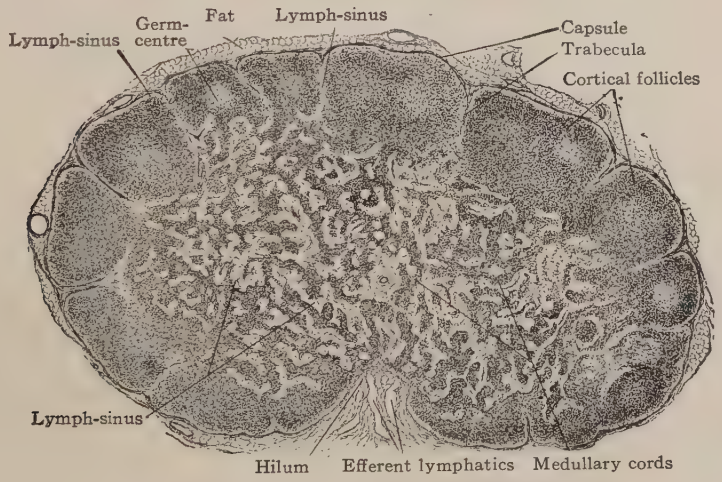


FIG. 154—Section of small lymph-node through hilum. × 23.

lymphatic vessels, sometimes singly, but often in chains or groups. On nearing a node, the lymph-vessel divides into a number of stems, the **afferent vessels,** which enter the substance of the node and communicate with the lymph-sinuses within its interior. From the latter other channels, the **efferent vessels,** arise and emerge from the node at a point usually, but not

always, marked by a slight depression, the **hilum.** The lymph-nodes are invested by a distinct fibrous **capsule,** in which elastic fibres and occasional unstriped muscle are present. From the inner surface of this envelope, the fibro-elastic tissue is continued into the substance of the node in the form of numerous radially directed trabeculæ, which thus subdivide the outer zone, or **cortex,** into a series of compartments. On reaching the inner limit of the cortical zone, the trabeculæ are less regular, and freely anastomose thereby breaking up the deeper parts of the node, the **medulla,** into uncertain cylindrical compartments. The spaces thus imperfectly defined by the trabeculæ

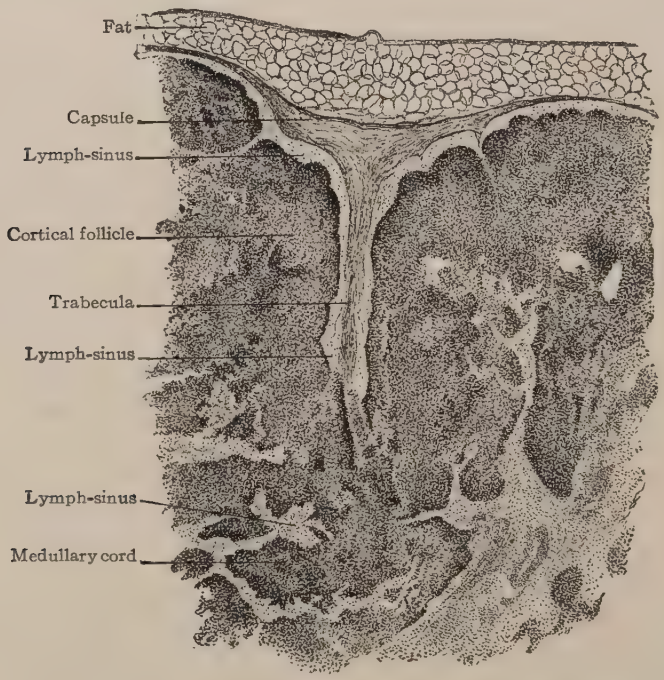


FIG. 155—Portion of periphery of lymph-node, showing relation between trabecula, sinus, and lymphoid tissue. × 50.

are incompletely filled by masses of compact lymphoid tissue, the general form and arrangement of which correspond to the compartments in which they lie. The masses contained within the peripheral spaces are irregularly spherical or pyramidal and constitute the **cortical nodules;** those within the intercommunicating central compartments form a network of irregular cylinders, the **medullary cords,** which are continuous with one another and with the deeper part of the cortical nodules (Fig. 154).

The intervals between the tracts of lymphoid tissue and the trabecular framework constitute a system of freely communicating channels, the **lymph-sinuses,** through which slowly passes the lymph brought to the node by the **afferent lymphatic vessels.** The latter pierce the capsule on the convex surface of the node and open into the sinuses that partially surround the

cortical nodules. After traversing the peripheral sinuses, the lymph passes into the irregular channels of the medulla and finally escapes from the node through the **efferent lymphatics,** which usually emerge at the hilum, if one be present, on the surface of the node opposite to the entrance of the afferent vessels. The lymph-sinuses, therefore, are bounded on one side by the capsule or trabeculæ and on the other by the masses of dense lymphoid tissue. The lumen of these channels, however, is not free, but occupied by a delicate wide-meshed reticulum consisting of fine strands of connective tissue where most marked, or of the anastomosing processes of stellate cells where very

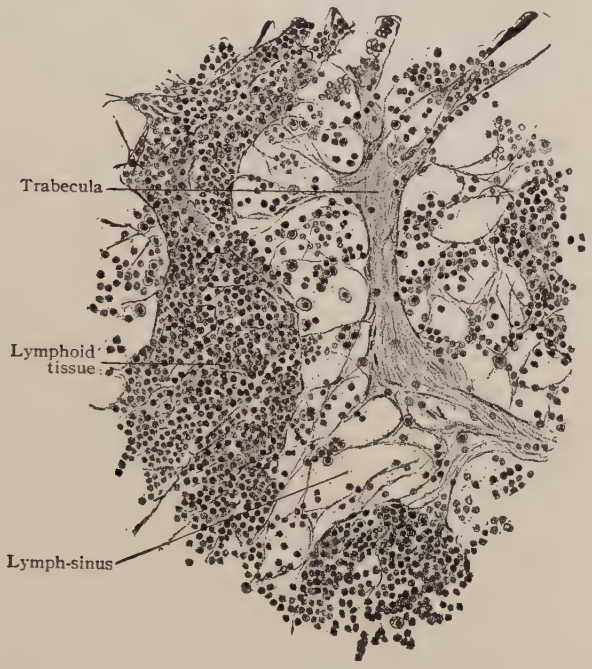


FIG. 156—Portion of medulla of lymph-node, showing details of lymph-sinus and medullary cords. ×250.

delicate. The sinuses are lined by an imperfect layer of flattened plate-like cells, that represent the endothelium of the adjoining lymphatic vessels. Although both the afferent and efferent lymphatics are provided with valves close to the node, none occur along the sinuses. The passage of the lymph through the node is retarded by the reticulum within the sinuses, thus favoring the process of phagocytosis, which is carried out both by the large free cells within the lymph-sinuses, the monocytes (also called macrophages and endotheliocytes), and by the fixed cells of the endothelium and reticulum. Here also young lymphocytes from the bordering lymphoid tissue enter the sluggishly moving lymph-stream. Germ-centres, the particular foci for the production of lymphocytes, usually are present within the cortical nodules, but are not found in the medullary cords.

The **blood-vessels** for the nutrition of the lymph-nodes are numerous. Some pierce the surface of the node at various points and are distributed to

FIG. 157—Cross-section of small lymph-node, injected to show rich vascular supply. × 10.

the capsule and the trabeculæ; most, however, enter through the hilum. After following for a short distance the trabeculæ, the arterioles cross the

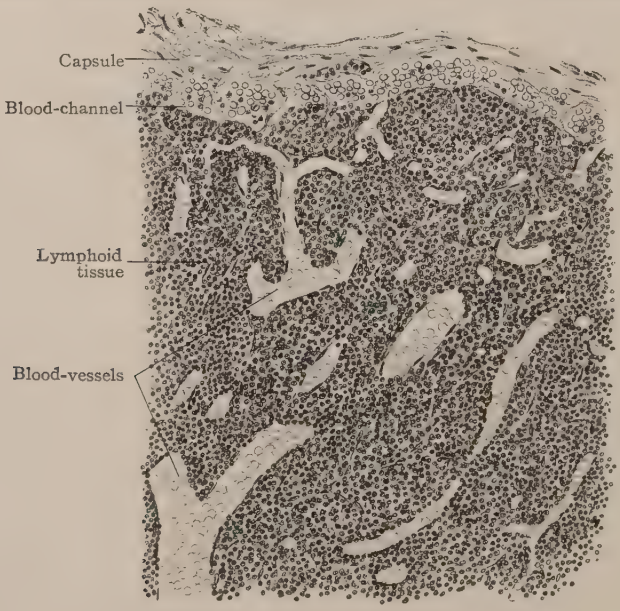


FIG. 158—Cortex of hemolymph-node, showing blood-channel beneath capsule.

sinuses and enter the cords and nodules of the denser lymphoid tissue, within which they break up into rich capillary networks.

The **nerves** enter the lymph-nodes at the hilum, in company with the

blood-vessels. They include both myelinated and unmyelinated fibres, but are chiefly sympathetic fibres destined for the involuntary muscle of the vessels and of the capsule.

Hemolymph-Nodes.—In addition to the ordinary lymph-nodes, there occur in various regions, especially in the prevertebral region of the abdomen, structures which resemble lymph-nodes in form and size, but differ from them in the deep red color which they usually exhibit. These bodies are known as the hemolymph-nodes. Their distinguishing feature is the substitution of blood-channels for the usual lymph-sinuses, which, in the typical hemolymph nodes, may be entirely wanting. Both cortical and medullary sinuses are seen to be filled with red blood-cells. The path of the blood resembles that within the spleen, since the blood-cells escape from the imperfectly walled vessels into the lymphoid tissue and thence pass into the blood-sinuses and on to the veins. In many cases, however, the substitution of the lymph-sinuses by blood-spaces is not complete, the sinuses occupying the central parts of the node with the spaces at the periphery. All gradations, in fact, are encountered, from the typical hemolymph-node at the one extreme to a lymph-node with enlarged blood-vessels, on the other. It has been suggested that hemolymph-nodes are all abnormal deviations from lymph-nodes. While these nodes share in the production of lymphocytes, they are probably seats of destruction of the erythrocytes, whose remains are seen in the phagocytes.

THE SPLEEN

The spleen lies far back on the left side in the abdominal cavity between the stomach and the diaphragm, and measures approximately five inches in

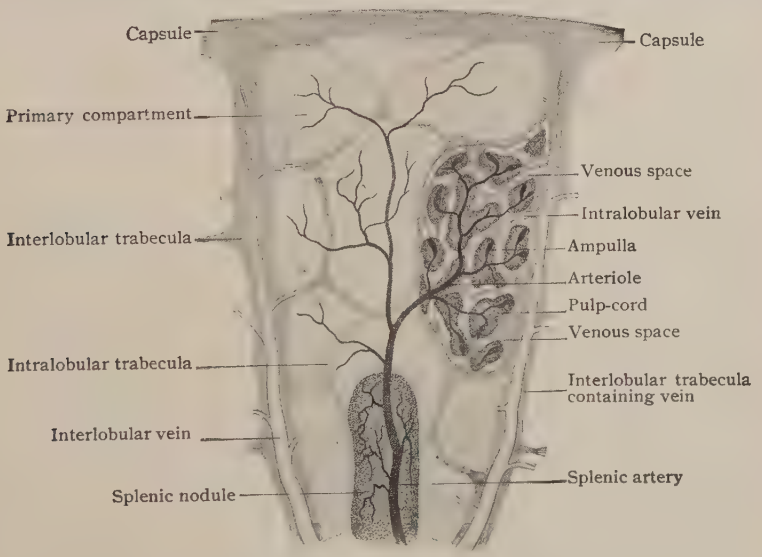


FIG. 159—Diagram illustrating architecture of a splenic unit; splenic pulp is represented in only one compartment. (*After Mall.*)

length and about three inches in width. Its form is variable and greatly influenced by the surrounding organs, since its substance is soft and yielding. It contains large quantities of blood and, hence, appears of a dark red or purple color. The spleen may be classed as a huge hemolymph-node, possessing the functions of producing lymphocytes and destroying erythrocytes.

The spleen is enclosed by a distinct **capsule,** which consists of bundles of dense fibrous tissue, numerous elastic fibres, and sparsely distributed bundles of unstriped muscle. With the exception of the hilum, the area between the peritoneal folds at which the splenic vessels and nerves enter or leave the organ, the outer surface of the capsule is united with the serous membrane, the peritoneum, which almost completely invests the spleen. At the hilum the tissue of the capsule is continued into the organ and sup-

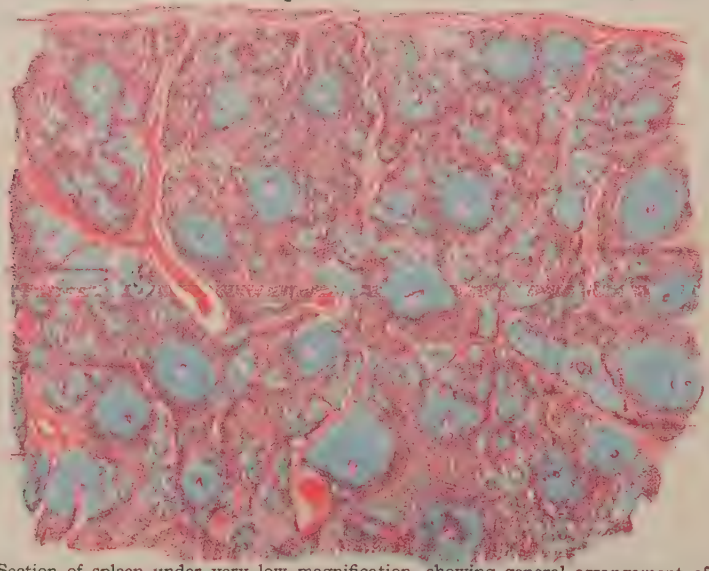


FIG. 160—Section of spleen under very low magnification, showing general arrangement of splenic tissue. × 10.

ports the blood-vessels and nerves. The capsule, furthermore, gives off from its deeper surface numerous processes, the **trabeculæ,** which pass into the substance of the organ and break up into innumerable delicate prolongations that unite to form the supporting fibrous **framework.** This framework is arranged with a certain degree of regularity, since the trabeculæ subdivide the spleen, at least its peripheral zone, into fairly regular compartments, the **splenic lobules** of Mall, about 1 mm. in diameter. Each of these units is imperfectly defined by three **interlobular trabeculæ,** from which secondary **intralobular processes** penetrate the lobule and subdivide the latter into about ten **primary compartments.** These, as well as the lobules themselves, are not isolated, but are freely continuous, since the intervening trabeculæ and processes form only incomplete partitions. The spaces within the fibrous framework are filled with the highly vascular lymphoid tissue, known as the **splenic pulp.**

The relation of the **blood-vessels** to the splenic lobules, although complex, is very definite. The branches of the splenic artery, after entering at the hilum and running some distance within the trabeculæ in company with the larger veins, break up into smaller vessels, each of which, parting from the vein, enters the proximal end of a lobule, through the middle of which it courses giving off twigs, one for each primary compartment of the lobule. On leaving the trabeculæ, the arteries carry with them prolongations of connective tissue, which, with the adventitiæ of the vessels, surround the latter with fibro-elastic coats of considerable thickness. Within these envelopes local accumulations of lymphoid cells (lymphocytes) occur and in consequence the arteries are surrounded by spherical or fusiform masses of dense lymphoid tissue, the **splenic nodules,** or **Malpighian bodies**. Depending upon the plane of section, these nodules appear in preparations of the spleen as irregular round or elongated, deeply-staining tracts, in which the artery

FIG. 161—Section of adult splenic nodule, showing its relations to surrounding pulp tissue. × 120.

usually lies somewhat eccentrically. During its course through the nodule, the artery gives off lateral branches which are resolved into capillaries that pierce as well as supply the ensheathing lymphoid tissue.

The terminal twigs of the artery are the small short vessels, known as the **pulp-arterioles**, which enter the anastomosing strands of lymphoid tissue, the **pulp-cords**, that, together with the blood-spaces, constitute the splenic pulp. The parenchyma of the spleen is thus composed of splenic nodules and spleen pulp. After repeated branching, the pulp-arterioles give rise to arterial **capillaries.** The arterial capillaries become directly continuous with enlarged thin-walled channels, the **ampullæ,** or **splenic sinuses,** which lie between the pulp-cords. These have fenestrated walls, and the endothelial cells are elongated and narrow, simulating involuntary muscle-fibres. These cells run lengthwise in the capillaries, and have slit-like spaces between them. Through these linear spaces some of the blood escapes into the splenic pulp, which thus becomes infiltrated with great numbers of erythrocytes and consequently appears of a deep red tint. After slowly welling through the pulp, during

which passage the effete erythrocytes, fragments of cells, and bacteria are ingested and destroyed by the phagocytic cells, the blood passes by narrow channels into the venous spaces and radicles forming the intralobular veins. It is possible also, that while one part of the blood brought to the spleen finds its way actually into the splenic pulp, another part may pass, by a closed path and under usual conditions, from the arteries into the veins, without mingling with the lymphoid elements of the splenic pulp. The **intralobular veins** are tributary to the larger **interlobular veins,** which occupy the interlobular trabeculæ and, finally, emerge at the hilum as the branches of the splenic vein.

The **splenic pulp** consists of an intricate complex made up of a delicate

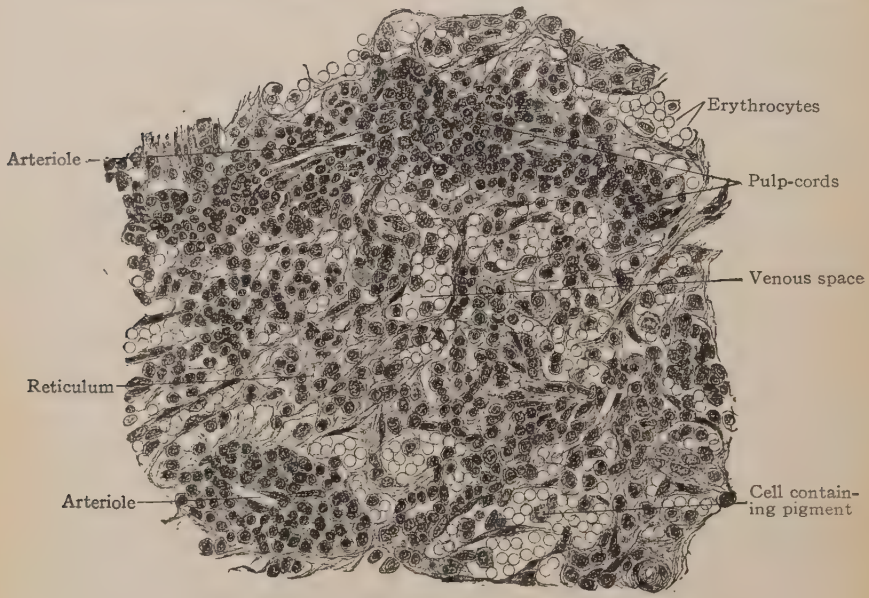


Fig. 162—Section of spleen, showing details of pulp-tissue. × 300.

supporting **reticulum,** continuous with the terminal ramifications of the intralobular trabeculæ, and the cells contained within and supported by the meshwork, together with the thin walled splenic sinuses and venous channels. The **pulp-cells** include a variety of elements, the most constant of which are (a) lymphocytes; (b) monocytes, here usually termed **splenocytes,** which are phagocytic cells containing evidences of disintegrating red blood-cells, or pigment particles derived from their hemoglobin; (c) granulocytes; (d) erythrocytes. A variable amount of free pigment from the disintegrated red cells is also present. During embryonic life, and perhaps latter in response to unusual demands for new red blood-cells (as after severe hemorrhage), the spleen is the site of origin of new red cells; these are at first nucleated, but soon lose their nuclei. The elements forming the imperfect endothelial lining of the ampullæ, or splenic sinuses, are peculiar in being elongated and possessed of nuclei which project into the lumina of the channels. The retic-

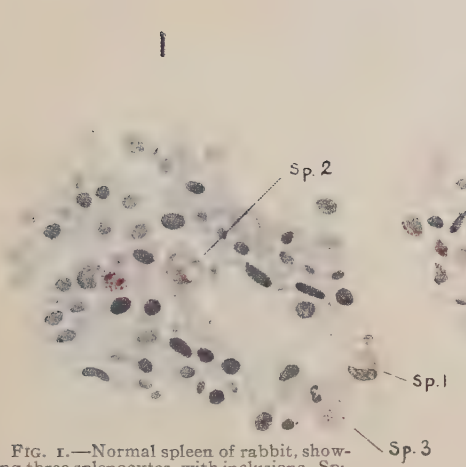


FIG. 1.—Normal spleen of rabbit, showing three splenocytes, with inclusions. Sp_1, splenocyte with single inclusion, colored with blood-pigment. Sp_2, splenocyte with several vacuole-like areas in its cytosome. Sp_3, splenocyte which had ingested several granular blood-cells.

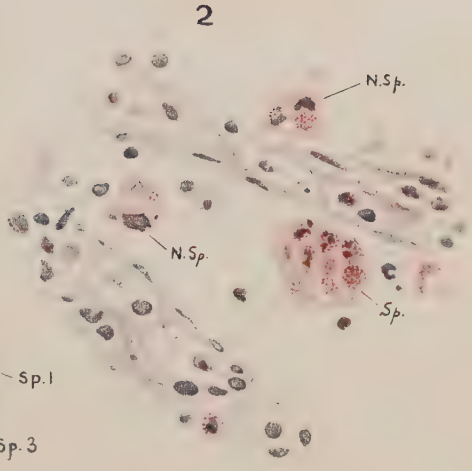


FIG. 2.—Spleen of rabbit, sixteen hours after injection of pigeon cells, showing three splenocytes with cellular inclusions. N.Sp., nucleus of splenocyte, with inclusions of granular blood-cells. Sp. splenocyte showing remains of nine cells which it had ingested.

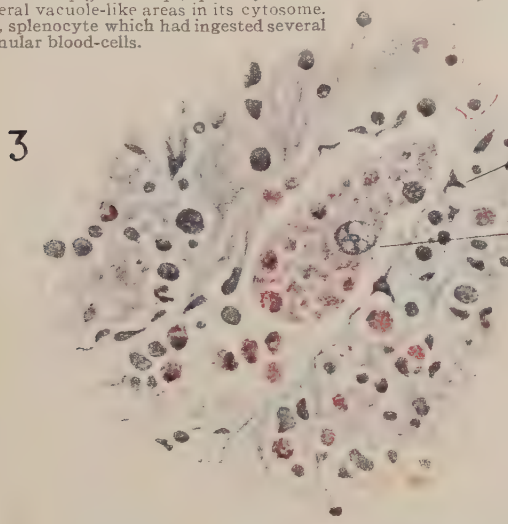


FIG. 3.—Spleen of same rabbit shown in figure 2. Shows a splenocyte greatly enlarged by the presence of numerous cells which had been ingested. N.Sp., splenocyte nucleus, enlarged. R, endothelial cell, of the reticulo-endothelial system.

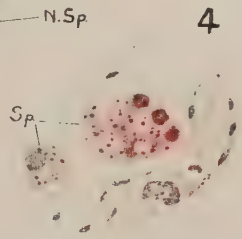


FIG. 4.—Spleen of rabbit, forty-eight hours after injection, showing two splenocytes, with inclusions. The splenocytes are now becoming smaller, as the process of ingestion and digestion of the cells, appearing in the blood as the result of the experiment, is nearly ended.

Spleen of rabbit, showing phagocytosis by splenocytes, within the blood-sinuses of the splenic pulp, under experimental conditions. Washed erythrocytes of pigeon were injected into the blood-stream of rabbits, through an ear vein. The hemolysis of the pigeon cells caused an outpouring of immature erythrocytes and granulocytes from the rabbits' marrow. Both the hemolysing pigeon cells and the immature rabbit cells were caught within the spleen and were phagocytosed, especially by the splenocytes. The spleens of the rabbits were examined at different intervals after the injection. ×575. (From Addison, *Am. J. Anat.* vol. 26, 1920.)

ular tissue is disposed around the splenic sinuses and venous radicles in rings which probably support and prevent collapse of the delicate channels. The splenic nodules correspond in structure with the cortical nodules of lymph-nodes and often enclose germ-centres. Since within the spleen many worn-out erythrocytes are destroyed and new lymphocytes are produced, it is evident that the blood carried away from the organ by the splenic vein is poorer in red and richer in white cells than that brought by the splenic artery.

The **lymphatics** are represented by a meagre set of superficial vessels, which lie beneath the serous membrane and converge towards the hilum.

The **nerves,** derived from the sympathetic solar plexus, include many unmyelinated fibres. For the most part they are sympathetic fibres destined for the unstriped muscle within the walls of the blood-vessels and within the trabeculæ. They enter at the hilum and accompany the branches of the splenic artery. Delicate unmyelinated fibres have been described within the splenic pulp, some of which are presumably sensory in function.

Accessory spleens are common, but they are not all of the same significance. Some are isolated parts of the spleen, which have become constricted and eventually separated. Others are seemingly independent masses of splenic tissue. Not a few have no splenic nodules and are intermediate between the spleen and the lymph-nodes, and, probably, are to be classed as hemolymph-nodes.

THE THYMUS BODY

Athough actually increasing in size and weight until towards puberty, the thymus body is essentially an organ of very early childhood, attaining its highest development about the second year. At that time it stretches from

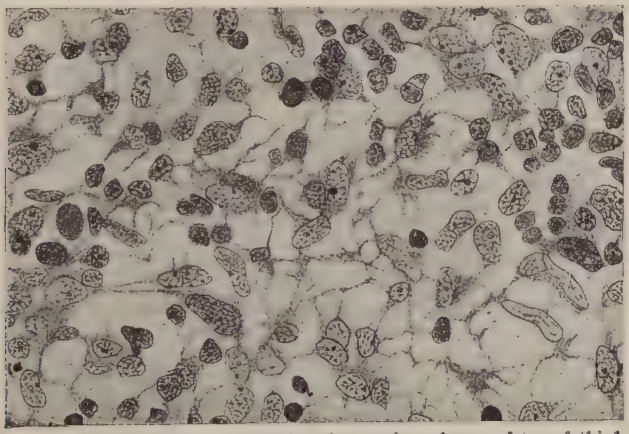


FIG. 163—Section of developing thymus from human fetus of third month; among the stellate reticulum-cells are seen the small thymic lymphocytes. × 690. (*Hammar.*)

the root of the neck downward into the thorax, behind the sternum and over in front of the pericardium, to about the line of the fourth costal cartilage. It is thickest above and descends as two flattened irregular lobes,

separated by fibrous tissue, of which the left one is more often the larger. Subsequently more or less extensive atrophy and replacement of the thymus tissue occurs, variable islands of the latter surrounded and invaded by fat cells being the usual condition of adolescence. Notwithstanding this replacement by adipose and connective tissue, the thymus never entirely disappears, remains of its tissue being present even in extreme old age.

The thymus body develops from varied epithelial outgrowths from the ventral wall of the third pharyngeal furrows. From these result long cylindrical masses of closely packed epithelial cells, which grow downwards and for a time enclose a lumen that later disappears. The masses increase by solid outgrowths, resembling those of an immature tubo-alveolar gland, so that by the middle of fetal life the organ has acquired a lobulated structure, a condition intensified by the ingrowth of vascular mesodermic tissue. Meanwhile, the original closely packed epithelial elements undergo marked

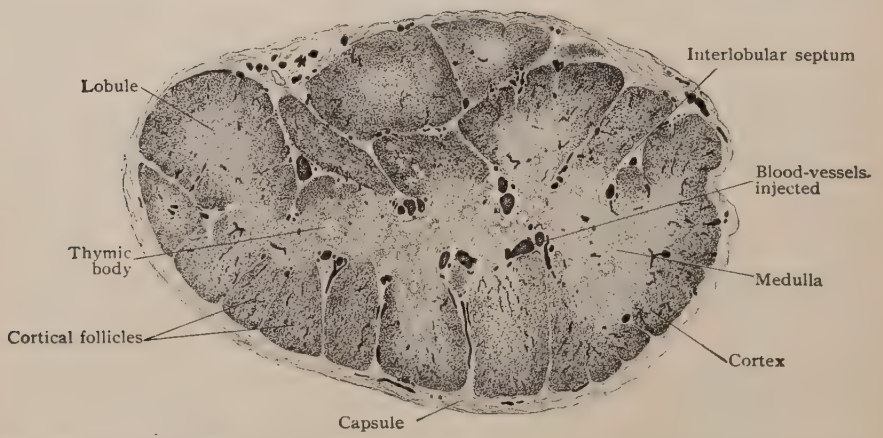


FIG. 164—Transverse section of lobe of thymus body of child, showing general arrangement of lobules. × 20.

change, most of them being converted into stellate cells that form a reticulum. From other cells arise by repeated division a profusion of very small cells that fill the meshes of the reticulum produced by the transformation just mentioned. The genetic relation of the small cells to the original entodermic epithelium is still disputed. According to Stöhr, Bell, and others, they arise from the epithelial elements; according to Hammar and others, they are mesodermic cells that early enter the thymus and correspond to true lymphocytes. All are agreed, however, that the "small cells"—the thymic lymphocytes—closely resemble, morphologically, the ordinary lymphocytes.

The thymus is invested by a loose fibro-elastic **capsule,** from which septa, rich in blood-vessels and lymphatics, pass inward and subdivide the organ into a number of indefinite **lobes.** The latter are broken up by partial partitions into **lobules,** in which a denser peripheral region, the **cortex**, and a lighter central one, the **medulla,** can be distinguished, although these divisions are often not sharply defined.

The **cortex** consists of closely packed small cells, the **lymphocytes,** (7–10 μ in diameter), whose cytoplasm is so meagre that the deeply staining nuclei are their most evident parts. The small cells are supported by a delicate meshwork formed by the stellate **reticulum-cells.** Numerous capillary blood-vessels, with accompanying scanty strands of fibrous tissue are intermingled with the cortical elements. The **medulla** is of looser texture and contains, in addition to the small and reticulum-cells, the irregularly spherical or elongated **thymic bodies,** or *corpuscles of Hassall,* which appear as small lighter areas scattered throughout the medulla. They first

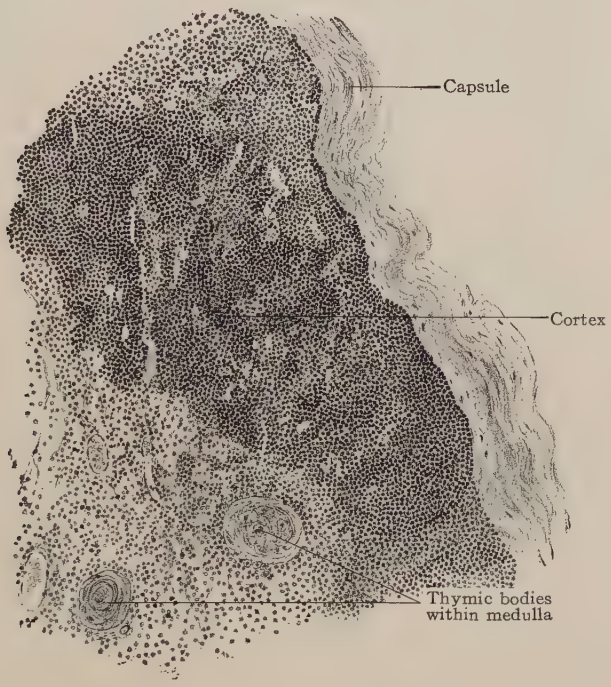


FIG. 165—Section of thymus, showing details of cortical and medullary substance. × 200.

appear about the middle of fetal life and increase in number and size until, at the end of the first year, they are plentiful and may attain a diameter of from .2–.3 mm., although usually they measure much less (40–60 μ). These bodies, present only in the medulla, are composed of large concentrically disposed epithelial elements, which, flattened and connected with the reticulum-cells at the periphery of the corpuscle, at its centre exhibit evidences of degeneration, such as nuclei poor in chromatin or disappearing, fusing of the cytoplasm of the central cells into an irregular homogeneous mass, or invasion of the cell by leucocytes. The centres of the bodies may enclose vacuoles containing fat, or mucus-reacting or colloid substance.

The significance and genetic relations of the thymic bodies have long been the subject of discussion. Formerly they were regarded as the remains of the original epithelial elements of the organ, all other parts being the products of the invading mesoderm. In the light of present embryological data, it is probable that the corpuscles result from the aggregation of hypertrophied and otherwise modified reticulum-cells and, therefore, that they are new and special formations, distinctive of the organ, and not merely the atrophic remains of the original epithelial elements. It is evident, however, that they are indirectly, through the reticulum-cells, derivatives of the primary epithelium. Since new corpuscles are being continually formed and those existing increase in size, during the active period of the thymus, it is possible that they are concerned in producing a substance serving some particular purpose during early life.

As age advances, the small cells become less numerous and the cortex markedly diminishes in thickness, so that the medullary substance comes into relation with the surrounding vascular interlobular connective tissue with increasing frequency and extent.

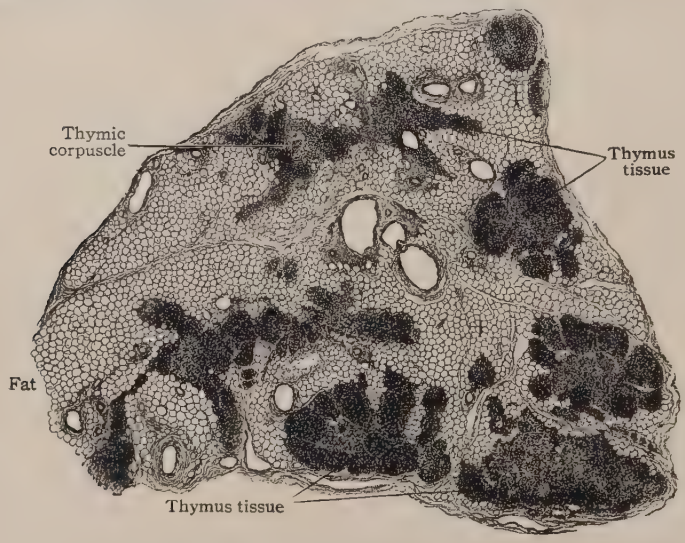


FIG. 166—Section of thymus body of man of twenty-eight, showing invasion and replacement of thymus tissue by fat. × 20.

At a variable time, in some cases before the second year and in others not until much later, an active general regression and atrophy of the thymus becomes established. The general process, however, is often antedated by reduction in the thymus, probably associated with impaired nutrition, whereby the number of the small lymphoid cells is greatly decreased and the distinction between cortex and medulla disappears. The medulla is the seat of occasional small cysts, of uncertain form and size, lined with epithelial elements that often bear groups of cilia-like processes. The thymus is not essential to life.

Coincident with the atrophy of the thymus tissue, fat cells progressively appear in the interlobular tracts, which latter, in consequence, become increasingly more voluminous, with separation of and encroachment upon the diminishing thymic tissue. Gradually the latter is replaced by the adipose tissue, until only isolated islands of the characteristic thymus tissue remain (Fig. 166). Complete disappearance of this structure, however, is very exceptional, even in advanced age a certain amount of it being recognizable upon microscopical examination.

The **blood-vessels** distributed to the thymus send their twigs into the organ in such manner that these lie at the junction of the cortex and medulla (Fig. 164). Capillaries thence proceed to the cortex and medulla, those within the former being more abundant than those distributed to the medulla. The venous radicles begin in the thymus stroma, some passing through the medulla while others become more directly tributaries of the interlobular veins. The **lymphatics** are represented by interlobular lymphatic vessels, that in turn drain into the large efferent trunks. The existence of intralobular passages, corresponding to lymph-sinuses, has not been established. The **nerves** are small and are derived from the sympathetic and the vagus. The fibres are traceable along the interlobular septa, in company with the blood-vessels, to whose walls they are chiefly distributed. A very meagre number of unmyelinated fibres have been described as terminating within the medulla as free endings.

MUCOUS MEMBRANES AND GLANDS

The apertures of the digestive, respiratory, and genito-urinary tracts on the surface of the body mark localities at which the integument becomes continuous with the walls of cavities and passages within. The linings of such spaces and tubes constitute **mucous membranes.** The latter, however, not only form the free surface of the chief tracts, but are continuous with the ducts and tubes leading into the **glands,** which are usually developed as outgrowths from the mucous membranes. These membranes line two great tracts, the **gastro-pulmonary** and the **genito-urinary.**

THE MUCOUS MEMBRANES

Every mucous membrane comprises two distinct parts: the **epithelium,** which forms the immediate free surface and protects the delicate subjacent structures, and the **tunica propria,** a connective tissue stroma which gives

FIG. 167—Section of oral mucous membrane, showing epithelium and tunica propria. × 300.

place and support to the terminal branches of the blood-vessels and nerves and the beginnings of the lymph-channels. A stratum of **submucous tissue,** ordinary loose and extensible, usually connects the mucous membrane with the surrounding structures.

The **epithelium** may be squamous or columnar, simple or stratified. Its character is determined largely by the conditions to which it is subjected or by its function. Thus, where a mucous membrane is exposed to the mechanical influences of foreign bodies, the epithelium is commonly stratified squamous, as in the upper part of the digestive tract. Where concerned in facilitating absorption, as in the intestinal tube, it is simple columnar in type. In localities in which the existence of a current favors the function of an organ, either as a means of freeing the surface from secretion or particles of foreign matter, as in the respiratory tract, or of propulsion through a tube, as in the

oviduct, the epithelium is of the ciliated columnar variety. Modifications of the epithelial cells, owing to the presence of pigment or of secretion, distinguish certain mucous membranes, as those of the olfactory region and the large intestine, respectively.

The **tunica propria** consists of a stroma of interlacing bundles of fibro-elastic connective tissue, supporting spindle-shaped or stellate connective tissue cells. The latter commonly lie against the walls of the interfascicular tissue-spaces that occur between the bundles of stroma-tissue. In many localities the outer surface of the tunica propria is beset with elevations, the **papillæ,** over which the epithelium extends. When slight, such irregularities may not modify the free surface of the mucous membrane, since the epithelium completely fills the depressions between the elevations. When more pronounced, the papillæ, or folds, of connective tissue produce conspicuous modelling of the surface, as seen in the papillæ of the tongue or the rugæ of the vagina. The papillæ contain the terminal loops of the blood-vessels and many of the endings of the sensory nerves. Where increase of surface is desirable, the mucous membrane may be thrown into cylindrical elevations, or **villi,** as conspicuously seen in the small intestine. In many places, particularly in the digestive tract, the mucous membrane contains more or less definite accumulations of lymphoid tissue, of varying size and complexity, as exemplified by the lymph-nodules within the vermiform appendix and the Peyer patches within the ileum. A more or less definite line separates the epithelium from the subjacent tunica propria. This demarcation is the **basement membrane,** or **membrana propria.** Often the basement membrane appears as a mere line beneath the epithelium and is derived by slight differentiation of the subepithelial connective tissue. Where, as around glandular tissue, it is well developed and appears as a definite homogeneous membrane, it is a product of the tunica propria. Exceptionally a reticular structure is recognizable. Sometimes the deepest stratum of the mucous membrane, next the submucous layer, is occupied by a narrow sheet of involuntary muscle, the **muscularis mucosæ.** While not everywhere present, it is well developed in the intestinal tract and in places consists of two distinct strata, a circular and a longitudinal. The muscularis mucosæ belongs to the mucous membrane and must not be confounded with the muscular coat proper which is often a conspicuous additional tunic.

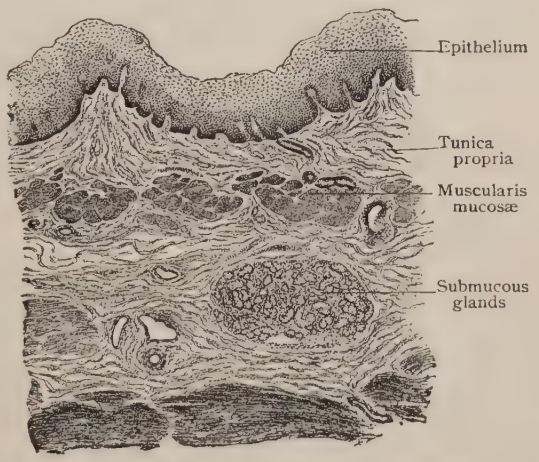


FIG. 168—Section of mucous membrane of œsophagus. × 55.

The **submucous layer,** the stratum of areolar tissue connecting the mucous membrane with the underlying structures, varies in thickness and density. Usually the attachment is a loose one and readily permits changes in position and tension of the mucous membrane; the latter, under such conditions, is often thrown into temporary folds, or rugæ, as in the œsophagus and stomach. In other places the folds are permanent and not effaced by distention of the organ, as conspicuously demonstrated by the plications in the duodenum in which the submucous tissue forms the basis of the band-like elevations.

The **blood-vessels** supplying mucous membranes reach the latter by

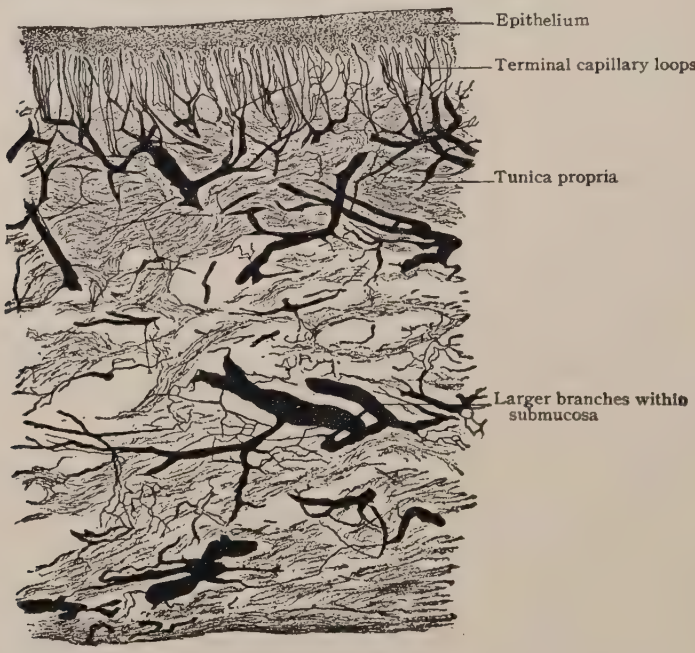


FIG. 169—Section of injected oral mucous membrane; the terminal capillary loops occupy the papillæ of the tunica propria and do not penetrate the epithelium. × 60.

way of the submucous tissue, in which the larger arterial branches divide into twigs that pass into the mucosa. Within the deeper parts of the tunica propria the arterioles break up into capillaries forming subepithelial and papillary networks, the vascular loops being limited to the connective tissue stroma. The veins usually follow the arteries in their general course. When glands are present, the capillaries surround the tubules or alveoli with rich networks, in close relation with the basement membrane. Towards the deeper parts of the mucosa, **lymphatics** exist as thin-walled channels which converge towards the submucous tissue. Within the latter the lymphatics form networks, provided with valves and beset with the accompanying dilatations.

The **nerves** distributed to mucous membranes include myelinated

fibres derived from the cranial or spinal trunks and unmyelinated fibres from the sympathetic ganglia. The sympathetic fibres are destined for the involuntary muscle of the blood-vessels and for the glands. The immediate supply of the involuntary muscle-cell is always the efferent postganglionic fibre (axone) from the sympathetic neurone which is thus the last link in the chain conducting the motor impulse. The position of the sympathetic cells varies, in some cases being remote and in others close to the muscle supplied. When near the mucous membrane, they occupy the microscopic ganglia within the submucous layer. Surfaces highly endowed with sensibility are generously provided with twigs containing myelinated fibres. As the latter approach their destination, they lose their myelin sheath and, as naked fibres, form subepithelial plexuses from which fibrils pass into the papillæ, where some terminate in free or special endings. Others enter the epithelium and penetrate between the cells for a variable distance to end free, for the most part, in minute bulbous swellings.

THE GLANDS

The simplest type of gland is the **unicellular gland** represented by the goblet-cells which occur in profusion in mucous membranes covered with columnar epithelium. The viscid secretion, or **mucus,** poured out by the goblet-cells serves to protect and lubricate the surface of the mucous membranes. The term "gland," however, commonly implies a more complex organ, composed of an aggregation of secretion-producing cells enclosed within connective tissue and provided with ducts and blood-vessels. These are externally secreting glands, or **exocrine** glands. They arise as outgrowths from the epithelium of mucous membranes and skin, some of the epithelial elements becoming modified into secretion-forming cells, others serving to line the efferent channels, through which the secretion is discharged. Examples of exocrine glands are the salivary glands, liver, pancreas, and the mammary glands.

In contrast to these are internally secreting glands, or **endocrine** glands. These differ from the usual type of gland in having no duct-system, and the glandular cells discharge their secretion into adjacent blood-capillaries and sinusoids. Thus in the endocrine glands, the blood-stream both brings to the gland-cells the materials, out of which the new substance, the secretion, is elaborated and also carries the secretion away. Examples of endocrine glands are thyroid, parathyroid, adrenal, and hypophysis cerebri. In the case of the last-named gland, the secretion of part of the organ also passes out into the cerebro-spinal fluid. Some of the endocrine glands arise from epithelial cells, but during their development they usually lose this connection. Others arise from mesenchyme cells, as in the case of the cortex of the adrenal, and the interstitial cells of the testis. The endocrine glands will be described later.

The externally secreting glands are classified according to the form and arrangement of their secreting units into two chief groups, the **tubular** and the **alveolar,** each of which occurs as **simple** or **compound.** In many instances, however, no sharp distinction between these conventional groups

exists, some important glands, as the salivary, being in fact a blending of the two types; such glands are, therefore, appropriately called **tubo-alveolar.**

In the least complex type, the simple tubular, the gland consists of a cylindrical depression lined with epithelium continuous with that covering the adjacent surface of the mucous membrane, as an outgrowth of which it is developed. In such simple glands the two fundamental parts, the **fundus** and the **duct,** are seen in their primary type. The fundus includes the deeper portion of the gland, in which the epithelium has assumed the secretory functions, the cells becoming larger in contrast to the narrower columnar cells of the duct. The duct connects the fundus with the free surface

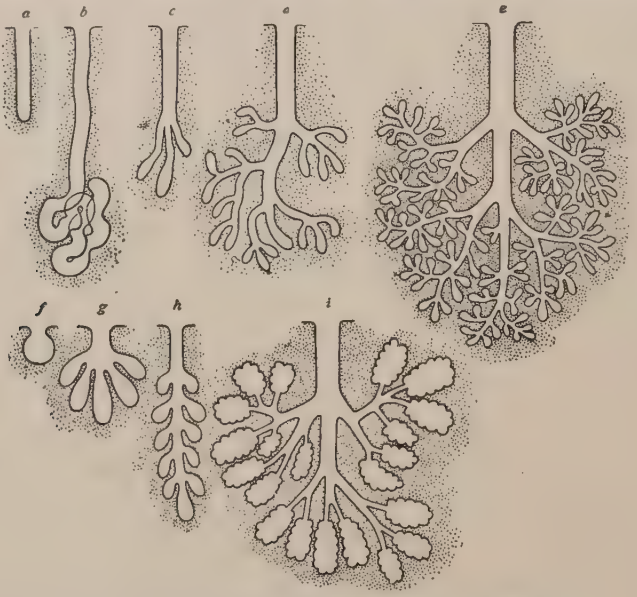


FIG. 170—Diagram illustrating types of glands. *a–e*, tubular; *f–i*, alveolar, or saccular. *a*, simple; *b*, coiled; *c*, *d*, increasingly complex compound tubular; *e*, tubo-alveolar; *f*, simple; *g*, *h*, *i*, progressively complex compound alveolar.

and carries off the secretion produced by the gland-cells. It is lined with columnar cells that take no part in secretion and near its outer end has the character of the adjoining surface epithelium. Dilatation of the fundus of the primitive type produces the simple alveolar, or saccular, gland; division of the fundus and part of the duct gives rise to the compound tubular variety; repeated subdivision of the duct, with moderate expansion of the associated terminal parts, leads to the production of the tubo-alveolar type.

Simple tubular glands may be minute cylindrical depressions of almost uniform diameter, as the intestinal glands in the small and large intestine, or they may be somewhat wavy and slightly expanded at the fundus, as seen in the gastric glands within the fundus of the stomach. When torsion becomes very pronounced, as in the sweat-glands, the **coiled gland** results.

Compound tubular glands present all degrees of complexity, from a simple bifurcation of the fundus and adjoining part of the duct, as in the pyloric glands, to the elaborate duct-system ending in tubular terminal divisions, conspicuously exampled in the kidney. The elongated terminal secreting units are ordinarily called gland-tubules.

Tubo-alveolar glands, modified compound tubular, constitute a very important group comprising many of the chief secretory organs of the body, as the salivary glands and pancreas. They are made up by the repetition of similar units, differences in the size of the organs depending upon the number of associated units. Each functional unit corresponds to the slightly enlarged fundus of a simple tubular gland and is termed an *alveolus* (or acinus). The alveoli, or acini, are formed of the secreting cells arranged around the **lumen** and are limited externally by a basement membrane which supports the glandular epithelium and separates the latter from the perialveolar blood-vessels. The alveoli belonging to the same terminal duct are held together by delicate connective tissue and constitute a pyramidal mass of glandular tissue, the *primary lobule*. The primary lobules are assembled into larger groups, the *secondary lobules*, which in turn are united by the interlobular connective tissue as the *lobes* of the gland. The lobes are held together, more or less firmly, by the interlobular areolar tissue continuous with the general fibrous envelope, or **capsule,** which invests the entire organ and separates it from the surrounding structures.

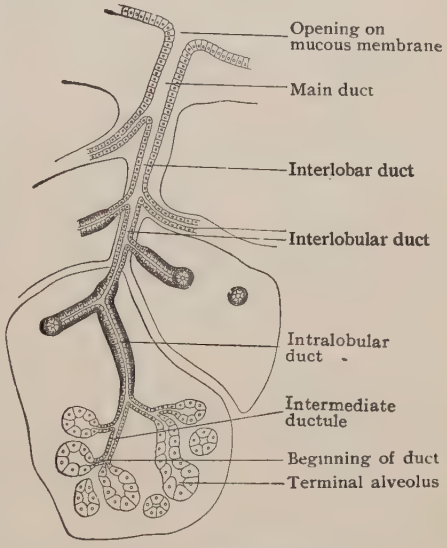


FIG. 171—Diagram illustrating relations of duct-system in glands of tubo-alveolar type.

The interlobar tissue and its interlobular continuations contain the blood-vessels, lymphatics, and nerves supplying the gland and, in addition, the major part of the system of duct-tubes. In the larger glands the ducts constitute an elaborate system of passages arranged after the general plan shown in the accompanying diagram (Fig. 171). Traced from the alveoli, the duct-system begins as a narrow canal, the **intermediate ductule** or **tubule,** lined with low cuboidal or flattened cells directly continuous with the glandular epithelium of the alveoli. After a short course the intermediate ductule increases in diameter and becomes the **intralobular duct,** which is often conspicuous on account of its tall and sometimes striated epithelium. The further path of the excretory passages lies within the connective tissue separating the divisions of the glandular substance and embraces the **interlobular** and the **interlobar ducts.** The latter join to form

the usually single main **excretory duct** which opens on the free surface of the mucous membrane. The excretory duct is lined for some distance by cells resembling those covering the adjoining mucous membrane; where these are stratified squamous in type, this character is retained for only a short distance within the duct, gradually giving place to the simple, sometimes at first double, layer of columnar epithelium which extends as far as the intralobular ducts. The walls of the larger ducts consist of a fibrous coat, containing much elastic tissue and lined by epithelium; in the large glands, as in the parotid, and pancreas, the walls are strengthened externally by a layer of unstriped muscle.

The **glandular epithelium** lining the alveoli rests upon the basement

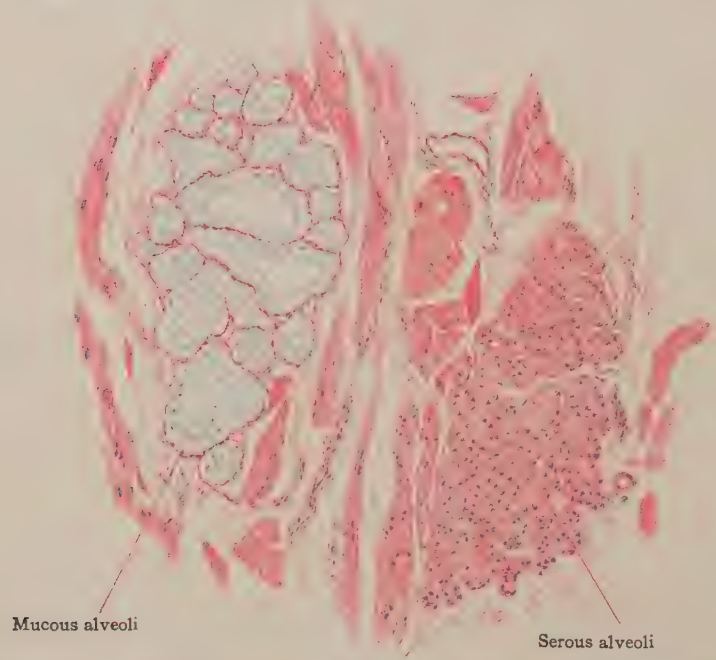


FIG. 172—Section of tongue, showing alveoli of serous and mucous types of glands. × 60.

membrane and usually consists of a single layer of spherical or polygonal secreting cells. The latter surround the lumen into which the product of the cells is poured and from which the secretion passes into the beginning of the duct. Depending upon the peculiarities of the cells and the character of their secretion, lubricating glands are divided into **serous** and **mucous.** It should be noted, however, that in many glands both serous and mucous cells occur, either within adjoining primary lobules, or, indeed, within the same alveolus.

The **serous glands** are distinguished by cells which are distinctly granular, somewhat pyramidal, and provided with nuclei situated near the centre. The secretion elaborated by such glands is thin and watery. The

general appearance of the cells depends upon the number and size of the particles, or droplets, of secretion stored within their cytoplasm, and changes markedly with the variations of functional activity of the gland. When a serous gland is at rest, its cells are loaded with secretion and appear, therefore, larger and coarsely granular. After active function, on the other hand, the cells are exhausted and appear smaller and almost free from granules, often exhibiting a differentiation into a clear outer zone devoid of granules and a darker inner zone, next the lumen, in which secretion-granules still remain.

The **mucous glands** elaborate a clear, viscid, homogeneous secretion, which when present in quantity, as during rest, distends the cells, crowding the nuclei against the basement membrane and giving the cells a clear and transparent character. When loaded and distended with secretion, the transparent cells have well-defined outlines and a narrow peripheral zone containing the displaced nucleus and granular cytoplasm. After prolonged activity, the exhausted cells contain relatively little secretion. In consequence, the cells lose their transparency and become smaller, darker and more granular than when the gland is resting.

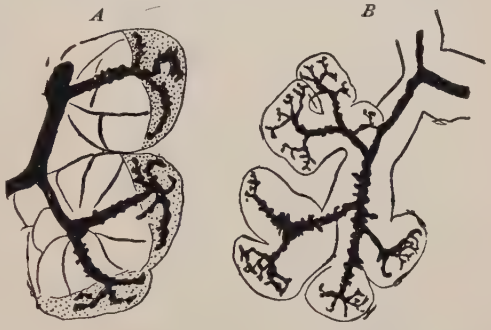


FIG. 173—Portions of salivary glands, showing terminal ducts and secretion-canaliculi: *A*, from submaxillary of dog—the canaliculi extend to the demilunes of serous cells; *B*, from submaxillary of rabbit—the canaliculi pass between the serous cells. × 500 and 290. (*Retzius.*)

The alveoli of mixed mucous glands often contain crescentic groups of small cells lying between the usual large clear elements and the basement membrane (Fig. 195). These are the **demilunes** and are aggregations of serous cells. In order to afford means of escape for their secretion, since the serous cells are excluded from the lumen of the alveolus by the mucous elements, minute intercellular channels, the **secretion-canaliculi,** pass from the main lumen to the demilunes (Fig. 173). Such secretion-canaliculi are not limited to mixed mucous glands, but are found in serous alveoli and in other glands containing isolated secreting cells, as in the fundus glands of the stomach (Fig. 201). Probably not all demilunes are composed of serous cells, since small groups of mucous cells, when containing little secretion, become peripherally displaced by the adjoining distended cells and then appear as crescents. These, however, are not provided with secretion canaliculi. Minute secretion-channels have been described within the cytoplasm of glandular epithelium, as the liver cells; it is undecided, however, as to what extent such **intracellular secretion-canaliculi** are preformed.

According to the proportions of the two types of alveoli, the tubo-alveolar glands have been arranged in four groups: (a) **pure serous glands,** in which only serous alveoli are present, as the parotid; (b) **mixed serous**

glands, in which a few mucous alveoli are intermingled with the serous, as in the submaxillary; (c) **mixed mucous glands,** in which the serous cells occur as demilunes, as in the sublingual and buccal; and (d) **pure mucous glands,** in which only mucous alveoli, without demilunes, are found, as in the palatal.

Simple alveolar glands in their typical flask-like form, abundant in the skin of the lower vertebrates, are represented by the simple sebaceous glands. The dilated sac-like fundus is lined with clear and distended cells, which become modified into duct-cells at the exit.

Compound alveolar glands consist of a number of saccular alveoli that open into a common duct, as in the case of the large sebaceous glands, and the tarsal glands of the eyelid; or they may be much more complex, being made up of a number of alveolar systems, the ducts of which join a large excretory passage. When of such composition they strongly resemble the tubo-alveolar type, the saccular character of the alveoli being the chief distinction. The parotid and the serous part of the submaxillary are regarded by some histologists as examples of compound alveolar glands. The lung affords a conspicuous example of the principle of the compound saccular type in its mode of development and the arrangement of the air-tubes and saccular terminal compartments.

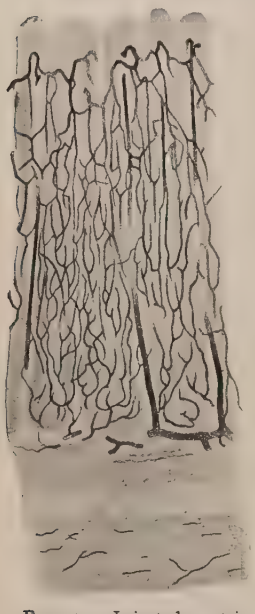


FIG. 174—Injected gastric mucous membrane, showing capillary network surrounding tubular glands. ×50.

The **blood-vessels** distributed to glands are always numerous, since an adequate blood-supply is necessary to bring to the gland-cells the materials from which their cytoplasm may select the substances required for their metabolism and secretory activity. In the case of the smaller and simpler glands, the capillaries of the mucous membrane form a mesh-work outside the basement membrane enclosing the glandular epithelium. The large compound glands are provided with vessels whose general arrangement corresponds with that of the duct-system, the blood-vessels following the tracts of interlobular connective tissue and its extensions between the alveoli. On reaching the latter the capillaries form networks that overlie the basement membrane and thus bring the blood-current into close relation with the secreting cells. When the relation between the capillaries and the cells is unusually intimate, as it is in the liver or the cortex of the suprarenal body, a basement membrane is wanting, a delicate reticulum and the wall of the vessel alone intervening between the blood-stream and the protoplasm of the cells. Although subject to local deviations, as in the liver, the veins follow the general course of the arteries, the larger blood-vessels, together with the duct-tubes, the lymphatics, and the nerves, occupying the tracts of connective tissue between the lobes and the lobules. The **lymphatics** are represented by the trunks which accompany the ducts within the interlobular tissue.

The **nerves** distributed to the larger glands include both myelinated and unmyelinated fibres which follow the arteries and ducts, around which they form plexuses. Along these strands, sympathetic ganglion-cells occur, sometimes singly but more often grouped, as microscopic ganglia from which sympathetic fibres proceed to the muscle of the blood-vessels and ducts, and to the alveoli. Upon reaching the latter, the unmyelinated fibres break up into end-plexuses surrounding the alveoli; the ultimate distribution includes **epilemmar** and **hypolemmar fibrillæ,** the former lying upon the latter beneath the basement membrane. The hypolemmar fibrillæ, derived from the extra-alveolar plexus, pass through the basement membrane and end in fine varicose threads between the gland-cells.

Development.—Since glands are only extensions of the mucous membrane or integument upon which they open, their development begins as an outgrowth, or budding, from the epithelium covering such surfaces. In the simple tubular glands the minute cylinders are closely placed and composed

FIG. 175—Portion of submaxillary gland of rabbit, showing distribution of nerves to the alveoli. ×290. (*Retzius.*)

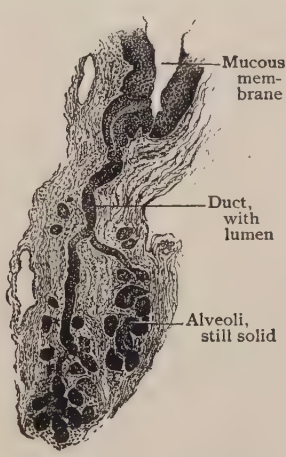


FIG. 176—Section of fetal oral mucous membrane, showing developing tubo-alveolar gland. ×50.

of densely packed cells. In the case of the larger compound glands, as the salivary or pancreas, the first anlage consists of a solid cylindrical plug which, penetrating into the mesoderm, soon begins to branch. The ends of the terminal divisions enlarge and eventually become the alveoli. Meanwhile the surrounding mesoblast undergoes condensation and forms the interlobular and other septa, as well as the general envelope, or capsule, thereby giving definite form to the glandular aggregation. The development of the gland involves a double process of active growth, the extension of the epithelial processes and a coincident subdivision of the latter by the mesoderm to form the units of the organ. The lumen of the gland appears first in the main excretory duct, from which it extends into the secondary tubes, and, finally, into the alveoli.

THE ALIMENTARY CANAL

This long and complicated tube, extending from the mouth to the anus, is developed from the entoderm with a mesodermic envelope, except at the two ends, each of which is at first a pouch lined by ectoderm. It consists of the mouth, pharynx, and œsophagus above the diaphragm; and of the stomach, and small and large intestine below the diaphragm. There are many accessory organs connected with the alimentary canal whose primary function is to assist in the processes of digestion. The most important of these above the diaphragm are the teeth, the tongue, and the salivary glands; those below the diaphragm are glands of various kinds, mostly so small as to be contained within the mucous membrane. Two large organs, however, the liver and the pancreas, belong to this class, both being primarily outgrowths from the early gut-tube. The general structural plan of the alimentary canal, presenting in places, however, great modifications, includes: (1) a lining of **mucous membrane;** (2) a **submucous layer** of connective tissue into which glands may penetrate from the mucosa; (3) a double layer of unstriped **muscle,** arranged, for the most part, as an inner circular and an outer longitudinal stratum; and below the diaphragm, (4) a **serous covering** from the peritoneum, which, although originally complete, is in the adult wanting in certain parts.

THE ORAL CAVITY

The Lips.—The histological transition from the skin covering the exterior of the lips to the oral mucous membrane takes place gradually, the two being connected by a broad intermediate zone which approximately corresponds to the red area of the margins of the lips. The lips, on both their outer and inner surfaces as well as on their free margins, are covered with stratified squamous epithelium, resting on fibro-elastic connective tissue. Thus the general elements of structure of both skin and mucous membrane are the same. There are, however, definite differences. The surface of the skin is relatively dry, being exposed to the air, while the surfaces of mucous membranes are moist, always being bathed by fluids. In the skin of the lip are the hair-follicles, with sebaceous glands and sweat glands. These are lacking in mucous membranes, but in the latter are usually small scattered glands. In the labial mucous membrane, these are mucous in nature, and are called labial glands. The central part of the lip is constituted of bundles of voluntary musculature principally of the orbicularis oris muscle.

The Oral Mucous Membrane.—The oral mucous membrane is everywhere covered with stratified squamous **epithelium,** from .2–.4 mm. in thickness (Fig. 167). When for any reason the large flat surface cells are not removed, as ordinarily they continually are by abrasion, they form a whitish semi-opaque film that masks the rosy tint of the oral mucosa. The **tunica**

propria consists of closely felted bundles of fibrous tissue and elastic fibres, and passes into the submucous stratum without sharp demarcation. Towards the surface supporting the epithelium, the bundles become more delicate and closer, so that the stroma acquires a less fibrous and more homogeneous appearance. The subepithelial border of the tunica propria is beset with innumerable elevations, the **papillæ,** which are especially well developed on free margins of the lips, the anterior part of the hard palate, and the gums. The papillæ of the tongue are special structures and will be described in

FIG. 177—Sagittal section of lip of young child, showing transition of skin into oral mucous membrane. × 20.

connection with the tongue. Within the elevations, which contain the vascular loops and nerves, the stroma is relatively compact and homogeneous. In addition to the ordinary connective tissue cells, wandering cells are frequently encountered within the stroma; the mast-cells, distinguished by their coarse basophilic granules, are particularly abundant in the gum, close to the neck of the tooth. The oral mucous membrane is attached to the surrounding bones and muscles by the **submucous layer,** a stratum of generally loose fibro-elastic tissue containing the larger blood-vessels, lymphatics, nerve-trunks, and the small oral glands. According to the amount and character of this layer the mobility of the oral lining varies. Where plentiful and loose, as over the floor of the mouth, the mucosa is

freely movable, while over the hard palate and the alveolar processes of the jaws the submucous tissue is so meagre that the mucous membrane is almost directly blended with the periosteum and correspondingly fixed.

The **blood-vessels** supplying the oral mucous membrane are numerous, the larger stems occupying the submucous layer, within which they form a wide-meshed network. Thence the twigs pass into the tunica propria, where they form a second and closer network. Their ultimate distribution includes capillary loops that occupy the papillæ, the smaller elevations containing only one or two terminal loops and the large ones a tuft of half a dozen or more. The **lymphatics** are represented by a network of tissue-spaces within the tunica propria which drain into the wide-meshed reticulum of definite lymph-channels within the submucous layer. The **nerves** are chiefly myelinated fibres that assume a loose plexiform arrangement within the submucosa. From here numerous twigs enter the tunica propria and break up into the component fibres, which mostly terminate in the stroma and papillæ either free or in connection with end-bulbs or tactile corpuscles. A few fibres, after losing the myelin sheath, penetrate the epithelium and, after repeated branching, end between the epithelial cells.

The Oral Glands.—In addition to the large salivary glands which, although pouring their secretion into the oral cavity, are situated outside of the immediate walls of the mouth, certain groups of glands, for the most part insignificant in size, lie within the oral wall and contribute secretions serving for the lubrication of the oral mucous membrane. Such oral glands include the labial within the lips, the buccal and the molar within the cheeks. The *labial glands* are very numerous and constitute an almost unbroken zone, something over a centimeter in width, that surrounds the oral cleft just inside the margin of the red lip-area. They are alveo-tubular in type, lie within the submucous layer, between the mucous membrane and the muscle and belong to the mixed mucous glands. The gland-cells, although chiefly mucous in character, include limited peripheral groups of serous cells arranged as demilunes beneath the basement membrane. The *buccal glands*, smaller and more scattered, occupy the submucosa beneath the buccinator muscle. They correspond in structure with the labial glands. The same is true of the *molar glands*, several small groups on the outer surface of the buccinator muscle. Their ducts pierce the cheek.

omit until later in quarter,

THE TEETH

In principle, the teeth may be regarded as hardened papillæ of the oral mucous membrane; they consist, therefore, of two fundamental parts, the connective tissue body, or core, and the epithelial capping. The primary tissues become greatly modified and give rise to the three constituents of the typical mammalian tooth, of which the **enamel** is derived from the ectodermic epithelium, and the **dentine,** with the pulp, and the **cementum** are produced by the mesoderm.

The Enamel.—This, the hardest tissue of the body, covers the crown, the part of the tooth projecting beyond the **gingivus,** or gum, and is thickest

on the cutting edge or grinding surface. It gradually thins off towards the *neck*, around which its terminal border appears as a wavy, or serrated, line. The remarkable hardness of the enamel is due to the excessive amount (97 per cent.) of earthy material and the small proportion (3 per cent.) of

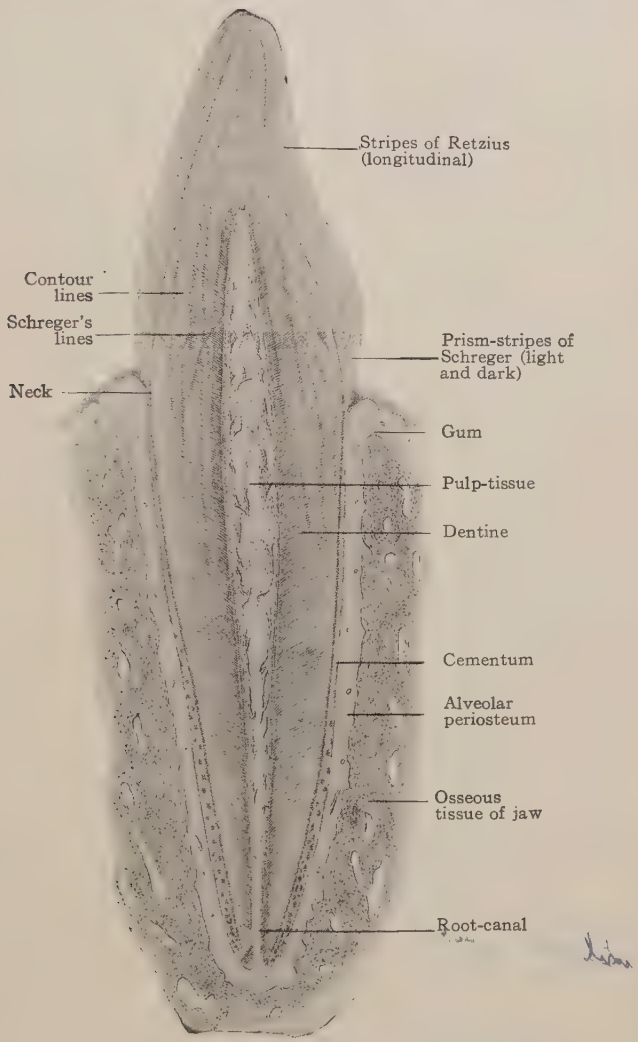


FIG. 178—Sagittal section of canine tooth in situ. Semidiagrammatic.

organic matter which it contains. The enamel—the product of epithelial cells, the **ameloblasts**—consists of an aggregation of five- or six-sided columnar elements, the **enamel-prisms,** which measure from 3–5 mm. in length and from 3–5 μ in width. Their general disposition is at right angles to both the surface of the dentine, upon which they rest, and the exterior surface of the crown. Since the prisms usually extend the entire thickness of the

enamel, they are of slightly larger diameter at the surface of the tooth than next the dentine. They run for a short distance almost at right angles to the surface of the dentine, then bend laterally for a considerable part of their course, but reassume a vertical path on approaching the external surface. In addition to these general curves, the enamel-prisms have a spiral arrangement, in consequence of which the parallelism of the prisms is disturbed, so that in thin ground sections, the prisms appear to be arranged in groups; all the prisms of any one group being cut in the same direction, but adjoining groups being cut in different directions. These groups are known as ranges of enamel-prisms, and indicate the interwoven character of their arrangement. These ranges are the basis of the prism-stripes of Schreger, to be described below. In thin, accurately transverse sections, enamel presents a mosaic of minute hexagons, which are the ends of the cut individual prisms. The outlines of the individual prisms are distinctly seen as dark or light lines, depending upon the focal adjustment. After careful decalcification and staining, the delicate lines defining the prisms are seen to be due to an inter-prismatic cementing substance. Particularly, but not necessarily, after the action of acids, the enamel-prisms in longitudinal sections exhibit alternate light and dark transverse markings with seemingly beaded, or varicose, outlines. These appearances are probably optical for the true outlines of the prisms are straight, the opposed surfaces of the adjoining columns being separated by a uniform thin layer of the cement-substance.

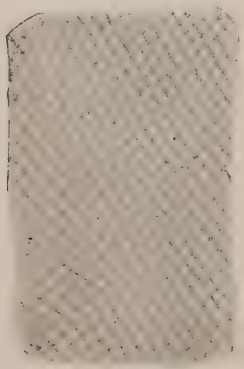


FIG. 179—Ground section of enamel, showing ranges of enamel-prisms. × 500.

When an axial longitudinal section of a ground tooth is examined by reflected, not transmitted, light, the enamel exhibits a series of alternate dark and light bands, known as the **prism-stripes of Schreger.** These markings (Fig. 178), depend upon the relation of the ranges of enamel-prisms to the axes of the rays of light. Each stripe includes from ten to twenty enamel-prisms, as may be seen by weak, transmitted light. In addition to the foregoing markings, the enamel often presents in radial longitudinal sections, brownish parallel lines, the **stripes of Retzius,** which correspond in their general direction with the contour of the tooth, but run at an angle of from 15° to 30° with the free surface. In cross-sections, these stripes are represented by a series of concentric lines encircling the crown parallel to and near the surface; in the middle and deeper parts of the enamel they are much less evident or entirely wanting. The significance of the stripes of Retzius is still disputed, but it is probable that they mark the advance of zones of calcification of the enamel-prisms during the growth of the enamel.

The **enamel-cuticle,** or *membrane of Nasmyth*, is a delicate envelope that completely invests the crown of the newly-erupted tooth. In the course of time it disappears from the areas exposed to wear, but over the protected surfaces it may persist throughout life. The membrane (from

2–4 μ in thickness) is transparent, structureless, resistant to the action of acids, less so to alkalies, and affords protection to the subjacent enamel. Since the cuticle is not only continuous with the cortical substance of the enamel-prisms, but also agrees with it in optical and chemical properties, the origin of the membrane may be referred to the enamel-producing elements, the epithelial cells forming the inner layer of the enamel-organ. After the completion of their work in producing the enamel-prisms, they produce a continuous envelope, which never undergoes calcification and remains as the enamel-cuticle.

The Dentine.—The dentine, or *ivory*, the substance which contributes

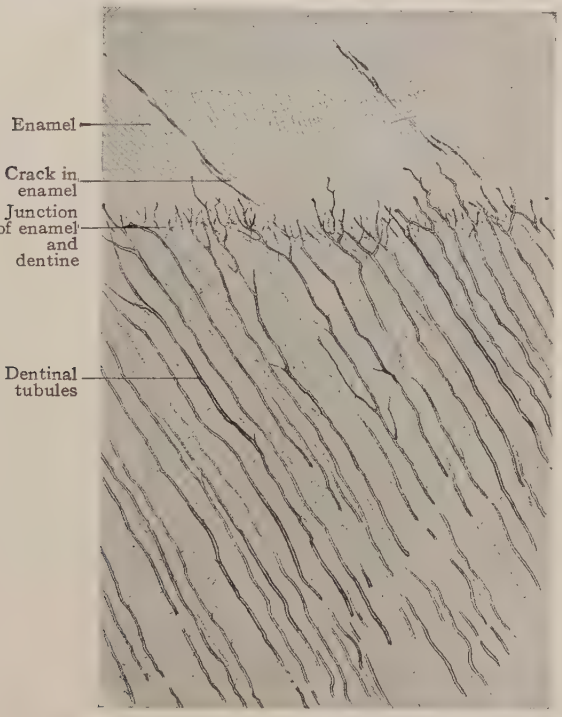


FIG. 180—Ground section of human tooth including adjoining enamel and dentine. × 280.

the bulk of the tooth, encloses the cavity containing the pulp and is itself surrounded by the enamel and the cementum. In both its genesis and chemical composition, dentine resembles bone, like the latter being a connective tissue modified by impregnation with lime-salts. Dentine exceeds bone in hardness and contains a larger proportion (72 per cent.) of earthy matter and a smaller amount (28 per cent.) of organic substance. After decalcification with acids, the remaining animal material retains the previous form of the dentine and yields gelatin on prolonged boiling in water. Dentine, like bone, is formed through the agency of specialized connective tissue cells, the **odontoblasts,** but differs from it in the fact that only

prolongations of the cytoplasm of these cells and not their cell-bodies become imprisoned in the intercellular matrix.

Examined in dried sections under low magnification, the dentine exhibits a radial striation, composed of fine dark lines which extend from the pulp-cavity internally, to the enamel or cementum, externally. These dark lines are the *dentinal tubules*, filled with air, which are homologous with the canaliculi of bone and contain the *dentinal fibres* as the processes of the odontoblasts are called. In the crown, as seen in longitudinal sections,

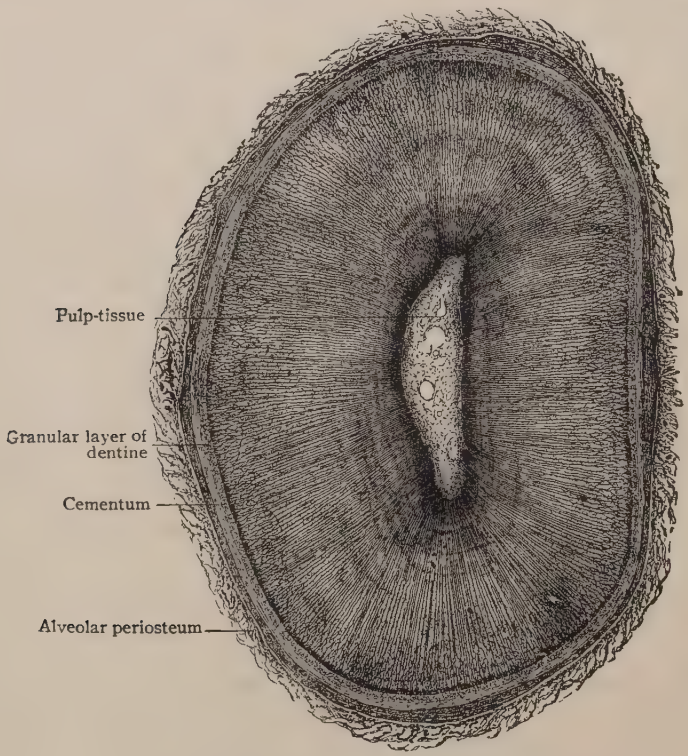


FIG. 181—Transverse section of root of lower canine tooth × 30.

the course of the dentinal tubules is radial to the pulp-cavity; in the body and fang their course is approximately horizontal and almost parallel. The canals, however, are not straight but wavy, the first bend being directed towards the root and the second towards the crown. In addition to these **primary curves,** especially marked in the crown, the tubules exhibit numerous shorter **secondary curves,** the whole arrangement imparting to the individual canals a spiral course. In consequence of the uniformity of these curvatures, the tooth-ivory displays a series of linear markings, **Schreger's lines**, which parallel the outer surface of the dentine. These markings, however, must not be confounded with another set of striæ, the **contour lines of Owen,** or the **incremental lines of Salter,** which, best seen in the crown,

run obliquely to the surface of the dentine (Fig. 178) and depend probably upon variations in calcification incident to the growth of the dentine.

The **dentinal tubules** are minute canals (from 1–2 μ in diameter), which begin at the pulp-cavity, where they are largest, and extend to the outer surface of the dentine, to end beneath the enamel or the cementum. Each spirally coursing canal undergoes branching of two kinds, a dichotomous division at an acute angle in the vicinity of the pulp-cavity, resulting in two canaliculi of equal diameter, and a lateral branching during the outer third of their course, whereby numerous tubuli of diminishing size are given off. The dentinal tubules are occupied by the **dentinal fibres,** the processes of the odontoblasts within the pulp, which in the young tooth are protoplasmic threads; later they lose this character and become harder and stiffer. The dentinal tubules differ in their mode of ending in the crown and the root. In the former situation, the outer surface of the dentine is indented with small crescentic depressions, filled with enamel, in which the tubules abruptly end, as if cut off. On the root, where the surface of the dentine is smooth and covered with cementum, the tubules end in curves or loops beneath the cementum, only in exceptional cases communicating with the canaliculi of the cementum. The immediate walls of the dentinal tubules are formed by delicate membranes, the **dentinal sheaths** of Neumann, which are specialized parts of the intertubular matrix of greater density and less complete calcification. After softening the decalcified dentine by alkalies, the sheaths may be isolated, since they resist the action of reagents which attack the surrounding substance.

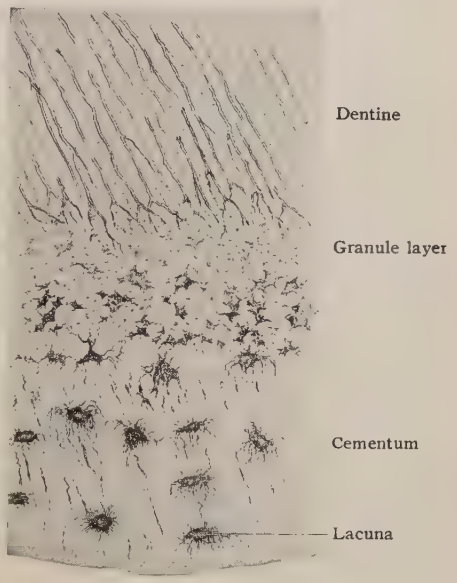


FIG. 182.—Ground section of root of dried tooth including adjoining dentine and cementum. × 300.

The intertubular **dentine-matrix** resembles that of bone in being composed of bundles of extremely delicate fibrous fibrillæ that swell on treatment with water containing acids or alkalies and yield gelatin after prolonged boiling in water. The disposition of the bundles of fibrillæ, more regular in dentine than in bone, is chiefly longitudinal and parallel to the primary surfaces of the dentine; additional bundles run obliquely crosswise in the layers of dentine. The bundles of fibrillæ, from 2–3 μ in diameter, appear in transverse sections as small punctated fields. The fibrillæ are knit together by the calcified ground-substance in which the lime-salts are deposited in the form of minute spheres, the interstices between the spherules

being later filled and calcification thus completed. When, as often happens, the calcification is imperfect, irregular clefts, the **interglobular spaces,** result. These spaces are bounded by the spherules, or **dentine-globules,** of calcareous material and are of irregular form and uncertain extent, being, however, usually largest in the crown. The junction of the dentine and cementum is always marked by a zone of closely placed interglobular spaces of small size; under low magnification in ground sections these spaces appear as dark granules, hence the zone is called the **granule layer** of Tomes.

The Cementum.—The cementum forms an investment that covers the outer surface of the dentine from the neck to the apex of the tooth. Beginning where the enamel ends, or overlapping the latter to a slight extent, the cementum extends as a thin homogeneous non-cellular sheath until near the apex of the root. Here it usually becomes thicker and shows lacunæ and canaliculi, which are in some respects like the similarly-named structures in bone. The matrix of the cementum differs from that of ordinary bone in containing slightly less organic matter and a greater number of fibre-bundles that run across the cementum. These bundles correspond to the fibres of Sharpey. The lacunæ are longer than those or ordinary bone and the canaliculi are unusually long and elaborate. As in bone, so in the cementum these spaces contain connective tissue elements, the **cementum-cells.** Although connecting with one another by means of the canaliculi, the lacunæ seldom communicate with the dentinal tubules, the latter commonly ending in loops or blind expansions. The outer surface of the cementum is intimately attached to the surrounding alveolar periosteum, the so-called **pericementum**, since from the latter the cementum is derived.

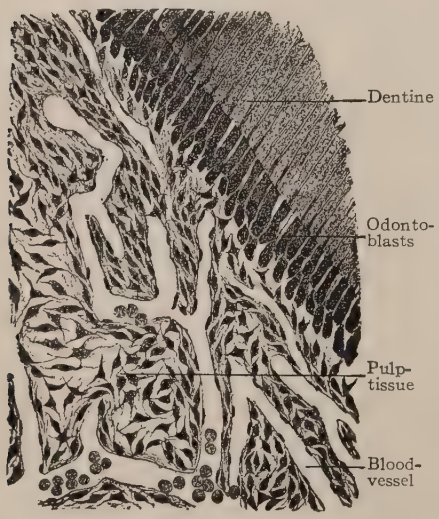


FIG. 183—Section of periphery of pulp-tissue of young tooth. × 175

The Alveolar Periosteum.—The periosteum investing the jaws also lines the sockets receiving the roots of the teeth, which are by this means securely held in place. The name, **pericementum** or **peridental membrane,** is often applied to this part of the periosteum which lines the bony alveoli on the one hand, and covers the cementum on the other and thereby fulfils the double rôle of periosteum and root-membrane. The alveolar periosteum is made up of tough bundles of fibrous tissue, elastic fibres being almost wanting, which are prolonged as the penetrating fibres into the cementum, on one side, and as the fibres of Sharpey into the alveolar wall, on the other. In the upper part of the root, the fibrous bundles are almost horizontal, but

towards the apex they are more oblique, the periosteum here losing its dense character and becoming a loose connective tissue through which the blood-vessels and nerves pass to the root-canal on their way to the pulp. At the alveolar border the pericementum is directly continuous with the stroma of the gum and immediately beneath the border of the enamel the fibrous bundles are consolidated into a dense band, the **ligamentum circulare dentis,** which still further aids in maintaining the firm union between the tooth and the alveolar wall. In addition to blood-vessels and nerves, within the pericementum are sometimes seen irregular groups of epithelial cells. The groups are the remains of the epithelial sheath of Hertwig which surrounded the young tooth during its early development.

The Pulp.—The contents of the pulp-cavity is the modified mesodermic tissue of the dental papilla remaining after the formation of the dentine. The adult pulp consists chiefly of soft highly vascular connective tissue, containing few or no elastic fibres but many irregularly distributed cells. The general type of the tissue resembles embryonal, both in its fibrous tissue and in its cells, the latter being round, oval, or stellate with long processes. The peripheral zone of the pulp, next the dentine, is of especial interest, since in this situation lie the direct descendants of the dentine-producing cells, the **odontoblasts.** These are tall columnar cells, arranged vertically to the surface of the pulp, about 25 μ in length and 5 μ in breadth, which send out long delicate processes, the **dentinal fibres,** into the dentinal tubules and short ones into the pulp-tissue. The spaces between the bases of the odontoblasts are occupied by smaller cells, less regularly disposed and less cylindrical and more irregular in form.

The **blood-vessels** supplying the pulp are from three to ten small arteries which break up into capillary networks soon after entering the pulp-cavity. In human teeth the capillaries usually do not invade the layer of odontoblasts. The larger veins, formed by thin-walled radicles, follow the general course of the arteries. **Lymphatics** have been recently demonstrated within the pulp as networks. The **nerves** supplying the pulp-tissue are numerous, each fang receiving a main stem and several additional smaller twigs, which in a general way accompany the blood-vessels. They include both myelinated and unmyelinated fibres, the latter being sympathetic fibres destined for the walls of the blood-vessels. On reaching the crown-pulp, the larger twigs are replaced by finer branches that subdivide into many fibres. These, on reaching the periphery of the pulp, form a plexus beneath the layer of odontoblasts from which unmyelinated fibres are given off. Some of these end beneath the odontoblasts in minute nodular swellings; others penetrate between the odontoblasts and terminate in pointed or bulbous free endings. Delicate fibres have been traced from the superficial pulp-nerves seemingly into the dentinal tubules.

DEVELOPMENT OF THE TEETH

About the beginning of the seventh week of fetal life, the ectodermic epithelium thickens along the margins of the oral opening and forms a band of proliferated epithelium, the **labio-dental strand.** This grows into the

surrounding mesoderm and divides into two plates which, while continuous at the surface, diverge almost at right angles at the deeper plane. The lateral, or outer, plate is vertical and corresponds to the plane of separation effected by the **labial furrow** that later occurs in differentiating the lips from the tissues forming the jaw. The median, or inner, plate grows more obliquely into the mesoderm and is the one directly concerned in the tooth-development; for this reason it is termed the **dental ledge.**

The anlages, or embryonic, rudiments of the milk-teeth are indicated by club-shaped epithelial outgrowths, which grow from the deeper surface of the dental ledge to form the **enamel-organs**. The bulbous end of the epithelial outgrowth increases rapidly and the mesenchyme which it grows against becomes more condensed than the surrounding mesenchyme. By further growth, the margins of the enamel-organ partially surround this denser mass of mesenchyme. As a result of this invaginated form, the enamel-organ assumes a three-layered arrangement; the mesenchyme which it caps is called a **dental papilla.** The enamel-organ remains attached for a time to the dental ledge by a broad strand of cells, which becomes more and more loosely arranged until, finally, it is broken and the enamel-organ is isolated from the oral epithelium.

The Dental Papilla.—This structure appears, shortly after the club-shaped enamel-organ begins to expand (Fig. 184, *C*), as a condensation of the mesoderm beneath the epithelial outgrowth. At first, the papilla consists of a close aggregation of small round proliferating cells, but later, coincidently with the differentiation of the three layers of the enamel-organ, the peripheral cells of the dental papilla become elongated and arranged as a continuous row of cylindrical cells, which cover the apical portion of the papilla and lie beneath the enamel-organ. These cylindrical mesodermic cells are the **odontoblasts,** the active agents in the production of the dentine. Where engaged in this process, particularly over the summit of the papilla, the cells measure from 35–50 μ in length and from 5–10 μ in breadth, but over the sides of the papilla they gradually become lower and less characteristic, until, at the base, they resemble the general cells of the papilla. As long as the tooth grows, odontoblasts are differentiated in the vicinity of the last-formed part of the root; after such differentiation the odontoblasts engage in producing dentine, and mitosis is no longer observed in these cells.

The **formation of the dentine** is accomplished through the agency of the odontoblasts in a manner related to that in which the osteoblasts produce the matrix of bone. The earliest dentine appears as a thin homogeneous stratum, the **prodentine,** which overlies the tip of the papilla and underlies the enamel-organ. This layer is resolvable into collagenous fibrillæ similar to those of bone-lamellæ. The **dentine-matrix,** deposited through the activity of the odontoblasts, is for a time uncalcified. The deposit of lime-salts occurs first over the apex of the papilla and next the enamel, a zone of uncalcified matrix around the pulp-cavity marking the youngest dentine. The calcareous material is deposited in the form of minute spheres, the **dentine-globules,** calcification being completed by the subsequent filling of the interglobular clefts. When for any reason calcification

is incomplete, these clefts remain uninvaded and are recognized as the interglobular spaces. The dentine-matrix differs from that of bone in being produced by a single set of cells, while the bone matrix is the collective work of relays of osteoblasts which, while contributing their increment, become imprisoned in the lacunæ within the matrix that they have formed. In human dentine, on the contrary, the odontoblasts remain on the surface and only exception-

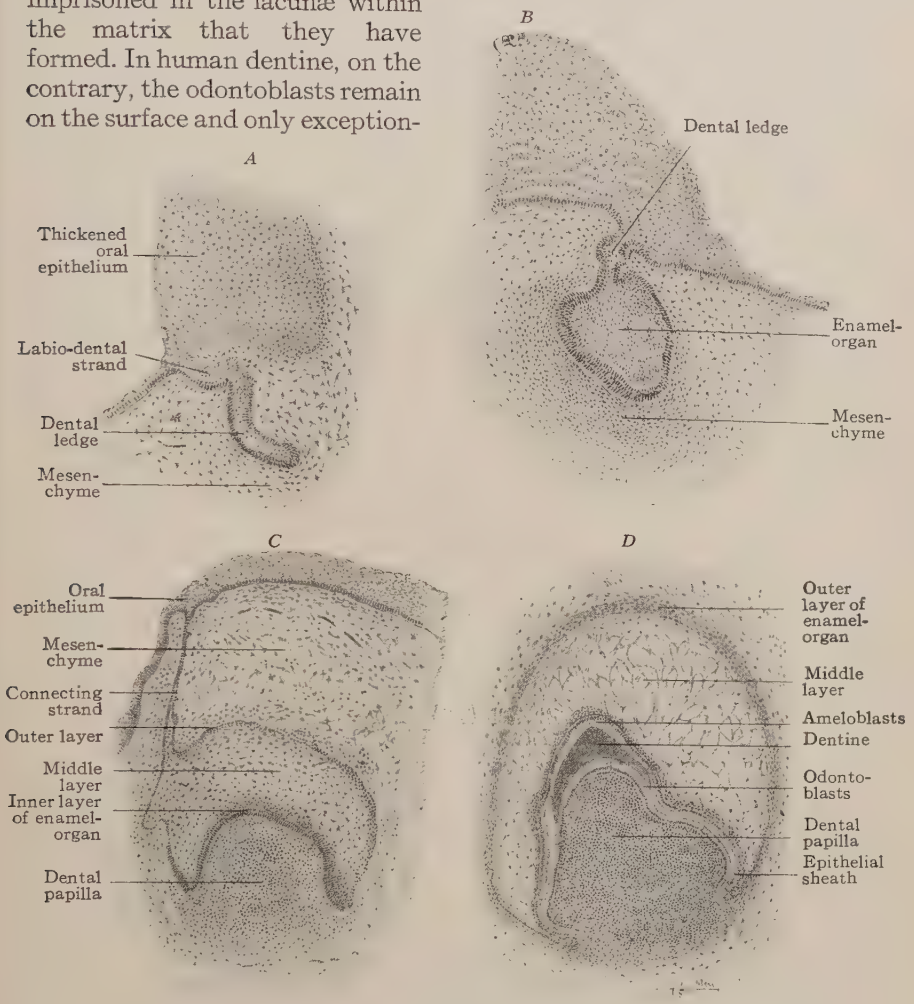


FIG. 184—Sections showing four early stages of tooth-developement. A, B, × 75; C, D, × 50

ally become enclosed within the dentine-matrix. With the completion of dentine-production, the odontoblasts become narrower and smaller and later exhibit evidences of impaired vitality. Their dentinal processes likewise grow thinner and less flexible and gradually assume the characteristics of the dentinal fibres. The portions of the dental papilla remaining after the dentine has been completed persist as the definite pulp-tissue, receiving a generous vascular and nervous supply.

The Enamel-Organ.—The end of the ectodermic epithelial outgrowth which early marks the position of the future tooth soon broadens, and through a process of unequal growth becomes cup-shaped and surrounds the top of the mesodermic dental papilla (Fig. 184). In contrast to the latter, which as the pulp-tissue partially persists as a permanent structure, the enamel-organ is only transient and ultimately disappears. When fully developed, the enamel-organ consists of three principal parts, the outer, middle, and inner layers, the outer and inner layers being directly continuous at the margin of the cup. The **outer layer** consists of flattened epithelial cells, which send processes into the surrounding vascular connective tissue

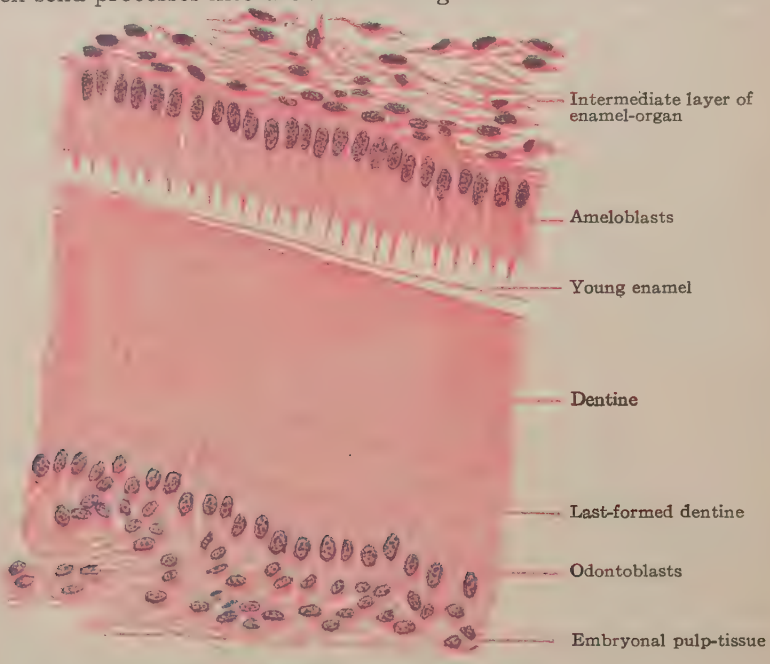


FIG. 185—Section of developing tooth through junction of enamel and dentine. × 400.

that invests the tooth-germ as the **dental sac.** These processes form papilla-like elevations and in the connective tissue between them is an abundant supply of blood-vessels, many of which penetrate the outer layer of the enamel-organ and run through the middle layer as far as the stratum intermedium. This condition is well shown in the enamel-organ of the developing molar of the new-born child. The **middle layer** or *stellate reticulum*, conspicuous by reason of its clear loose texture, consists of epithelial elements that have become highly modified in consequence of an enormous distention of the intercellular clefts by fluid, the epithelial plates in this manner being reduced to stellate cells connected by delicate processes. The inner border of this peculiar area constitutes a transitional zone known as the **intermediate layer,** in which the cells are rather densely arranged, several rows in thickness. This is best marked over the upper part of the

crown, at the sides thinning out and entirely disappearing at the margin of the enamel-organ. The **inner layer** of the enamel-organ comprises a single row of closely set tall columnar elements, the **enamel-cells,** also called **adamantoblasts** or **ameloblasts,** through whose active agency the enamel is produced. The ameloblasts are best developed over the top of the dental papilla, where they measure from 25–40 μ in length and from 4–7 μ in breadth. They possess oval nuclei that usually lie close to the basal ends of the cells. The ameloblasts are united by a small amount of cement-substance and defined from the intermediate layer by a distinct border. Over the sides of the dental papilla, corresponding to the lateral limit of the future crown, the ameloblasts gradually diminish in height until they are replaced by low cuboidal cells which, at the margin of the enamel-organ, are continuous with the epithelium of the outer layer. Preparatory to the formation of the dentine of the root of the tooth, this margin of the enamel-organ grows towards the base of the elongating dental papilla, which is in consequence embraced by the extension of the enamel-organ. This investment is known as the **epithelial sheath** of Hertwig (Fig. 184, *D*), a structure of importance in determining the form of the tooth, since it serves as a mould in which the dentine is deposited; there is, however, insufficient evidence to regard the epithelial sheath as an active or even necessary factor in the production of the dentine.

The **formation of the enamel** results from the activity of ectodermic epithelium and may be regarded as a cuticular development carried on by the ameloblasts. The initial phase in the production of the enamel is the appearance of a delicate cuticular zone at the inner end of each ameloblast. In this zone are deposited the materials for the enamel-rod, which will be produced by each ameloblast. The material becomes more and more condensed in character until it separates from the ameloblast as the beginning of the enamel-rod and the deposit of material begins again in the end of the ameloblast. By successive repetitions of this process, the enamel-rods are built up. Thus, the developing enamel increases in thickness by the addition of the increments formed at the inner ends of the ameloblasts, the same cells sufficing for the production of the entire tissue. The earliest formed enamel lies in apposition with the earliest formed dentine, the youngest enamel immediately beneath the ameloblasts. The enamel is deposited, therefore, from within outwards, or in the reverse of the direction followed by the growth of the dentine. The oldest strata of both substances lie in contact; the youngest on the outer and inner surfaces of the tooth. After the requisite amount of enamel has been produced, differentiation into prisms ceases; consequently the last formed enamel remains as a continuous homogeneous layer which invests the free surface of the crown and constitutes the enamel-cuticle, or membrane of Nasmyth.

The Tooth-Sac.—Coincidently with the development of the enamel-organ and the growth of the dental papilla, the surrounding mesoderm differentiates into a connective tissue envelope known as the dental or tooth-sac. The latter not only closely invests the enamel-organ, but is intimately related to the base of the dental papilla. The inner part of the tooth-sac is

abundantly provided with capillaries and is, therefore, an important source of nutrition for the growing dental-germ. The part of the sac opposite the root of the young tooth at first is prevented from coming into contact with the dentine by the double layer interposed by the epithelial sheath. This relation continues until the cementum begins to develop, when the vascular tissue of the dental sac breaks through the epithelial sheath to reach the outer surface of the dentine, upon which the cementum is deposited. In consequence of this invasion the epithelial sheath is broken up into small groups, or nests, of cells that persist for a long time as the epithelial islands encountered within the fibrous tissue of the alveolar periosteum, into which the dental sac is converted. As development proceeds, the tissue of the tooth-sac becomes denser, the part opposite the root persisting as the pericementum, while the superficial part blends with the tissue forming the gum.

The **formation of the cementum** is brought about through the agency of mesodermic tissue in a manner somewhat similar to that seen in the development of subperiosteal bone, the cement-producing cells, the **cementoblasts,** corresponding to osteoblasts, and bringing about a deposit of matrix upon the surface of the dentine. The cementum appears first in the vicinity of the neck of the tooth and thence progresses towards the apex of the root, as the dentine of the fang is formed. The layer of cementum is thickest at the apex, which it invests except where the canal or canals remain for the blood-vessels and nerves that pass to the pulp-cavity.

Provision for the **development of the permanent teeth** is made by the early differentiation of a second set of dental rudiments during the growth of the first. This includes the outgrowth of the enamel-organs of the second dentition from the dental ledge and the subsequent appearance of new dental papillæ from the mesoderm. The enamel-organ for the first permanent molar appears about the seventeenth week of fetal life and is soon followed by the corresponding dental papilla. The germs of the permanent incisors and canines, including the papillæ, are formed about the twenty-ninth week and those for the premolars about one month later. The enamel-organ of the second permanent molar appears about four months after birth and the papilla about two months later, while the enamel-sac for the third molar, which forms about the third year, precedes its papilla by almost two years. It is evident, therefore, that the development of these teeth proceeds very slowly, the embryonal structures being present years before the eruption of the permanent teeth. The presence of the milk teeth and of the germs of the permanent ones results in excessive crowding in the jaws during the fifth year. In order to accommodate the representatives of both sets, the crowns of the permanent teeth press between and against the roots of the milk teeth, which then undergo absorption. The latter process is effected by connective tissue cells, the **odontoclasts,** in a manner similar to that by which bone is removed by the osteoclasts. In consequence, before the temporary tooth is displaced it often is reduced to little more than the crown. Not until sometime after eruption are the roots of the permanent teeth fully formed.

THE TONGUE

The tongue is essentially a complex mass of striped muscle, the free surfaces of which are covered by an extension of the mucous membrane lining the mouth and the pharynx.

The **muscles** of the tongue include two groups, the **extrinsic** and the **intrinsic.** The former (the genio-glossus, the hyo-glossus, the stylo-glossus, and the palato-glossus) are all paired and extend from the skull or the hyoid bone to the tongue; the latter comprise the particular muscle, the **lingualis,** forming the chief mass of the organ. The tongue is incompletely divided into symmetrical halves by a vertical partition of dense connective tissue, the **septum linguæ,** which extends from the hyoid bone behind to the tip of the tongue, but fades away before reaching the apex. It is much better developed in the middle third of the tongue than at the ends, but even here the septum

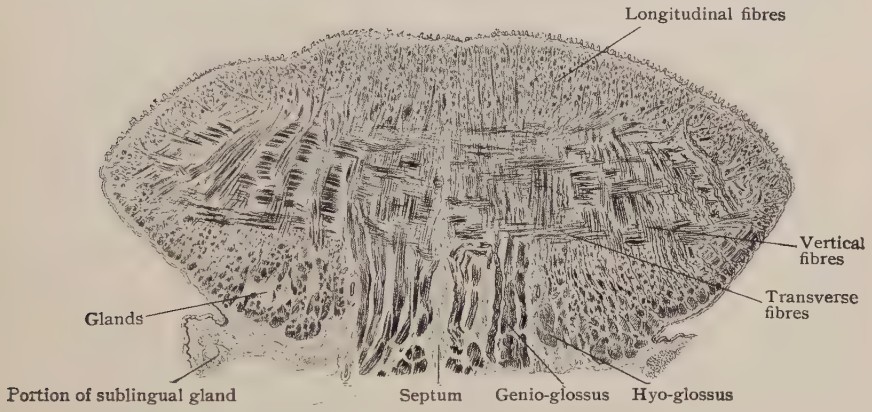


FIG. 186—Transverse section of child's tongue, through middle third. × 3.

falls short of the dorsal mucous membrane by a few millimeters. On viewing with low magnification a cross-section of the tongue at its middle third (Fig. 186), the intricate feltwork of muscle-fibres is seen to comprise fibres running in three general directions—longitudinal, vertical, and transverse. The **longitudinal fibres** appear transversely sectioned and form a well-marked superficial, or cortical, layer, some 5 mm. thick, immediately beneath the scanty submucous tissue covering the dorsum. These fibres include the principal part of the lingualis muscle, supplemented by fibres from the stylo-glossus. The **vertical fibres,** most conspicuous as the deeply placed and obliquely cut masses of the genio-glossus on either side of the septum, radiate towards the dorsal surface, where the lingual bundles end in the sub-mucous layer. The **transverse fibres** are entirely from the lingualis with the exception of those contributed by the palato-glossus. They arise from the septum and interlace with the vertical and longitudinal bundles; on approaching the mucosa they break up into strands which find their way between the superficial longitudinal fibres to a submucous insertion.

Branching is a peculiarity exhibited by many muscle-fibres that end in the submucosa.

The **mucous membrane** of the tongue corresponds in general structure with that lining the adjacent surfaces of the mouth and pharynx in consisting of the epithelium, the tunica propria, and the submucous layer. Over the sides and under surface of the tongue it is thin and smooth, with small papillæ towards the tip; on the dorsum the mucous membrane is greatly modified and presents characteristic appearances. The dorsal surface, moreover, includes two areas, the **papillary** and the **lymphoid,** which exhibit very different details.

The **papillary area** comprises the anterior two thirds, the lymphoid the posterior third. In the infant's tongue the junction of these areas is

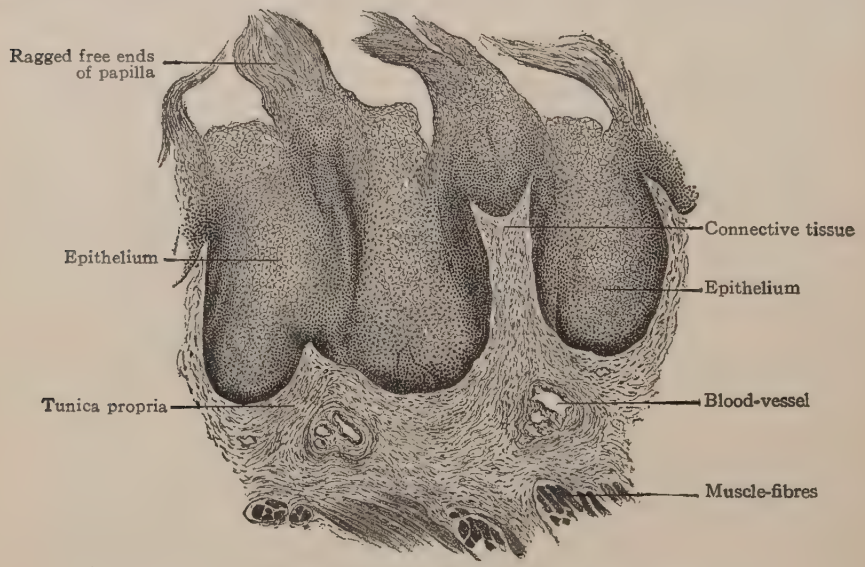


FIG. 187—Section of lingual mucous membrane showing filiform papillæ. ×75.

marked by a V-shaped groove, the **sulcus terminalis,** but this disappears and later the boundary is indicated by the conspicuous row of circumvallate papillæ. The anterior area is everywhere beset with elevations, the **papillæ,** which are of three varieties—the filiform, the fungiform, and the circumvallate. The **filiform,** or **conical, papillæ,** so abundant as to impart a velvety appearance to the tongue, are conical or cylindrical elevations of the tunica propria, composed of fibrous connective tissue with many elastic fibres and covered by a thick stratum of epithelium. The surface of the connective tissue core bears a number of small secondary papillæ, which, however, do not model the free surface of the mucous membrane. The filiform papillæ vary from .5–2.5 mm. in height and often end in brush-like strands of horny epithelial cells. The **fungiform papillæ** are far less numerous than the filiform and appear during life as red points in consequence of their thinner epithelium. As implied by their name, they are more or less mushroom-like

in form and vary from .5–1.5 mm. in height. The connective tissue core is beset with a number of secondary papillæ, over which stretches a smooth layer of epithelium. The latter contains occasional taste-buds. The **circum-**

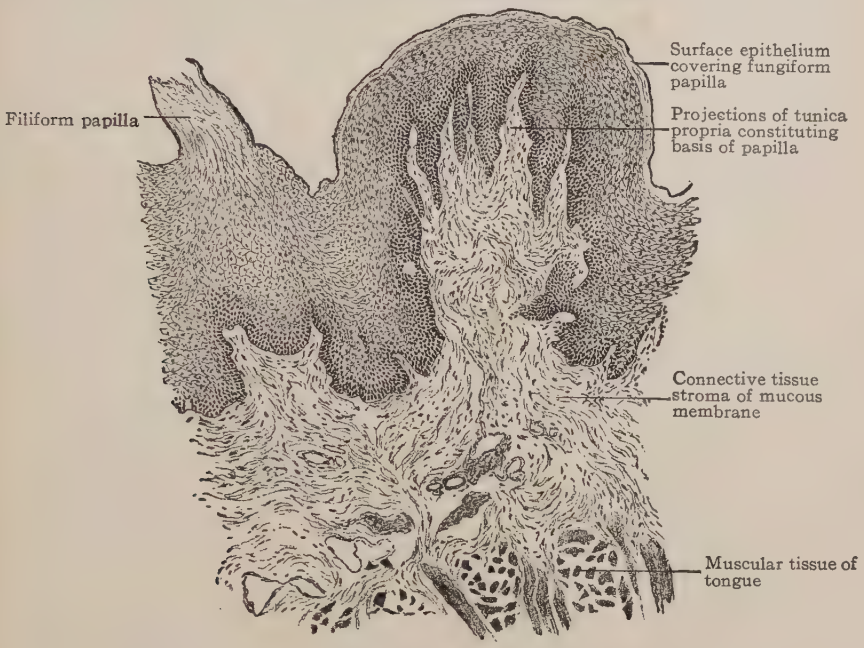

Surface epithelium covering fungiform papilla
Filiform papilla
Projections of tunica propria constituting basis of papilla
Connective tissue stroma of mucous membrane
Muscular tissue of tongue

FIG. 188—Section of lingual mucous membrane, showing fungiform papilla. × 75.

vallate papillæ, the most conspicuous of these elevations, usually number nine or ten, six and sixteen being the extremes. They are disposed as an irregular **V**, with the apex of the group directed backwards. These eleva-

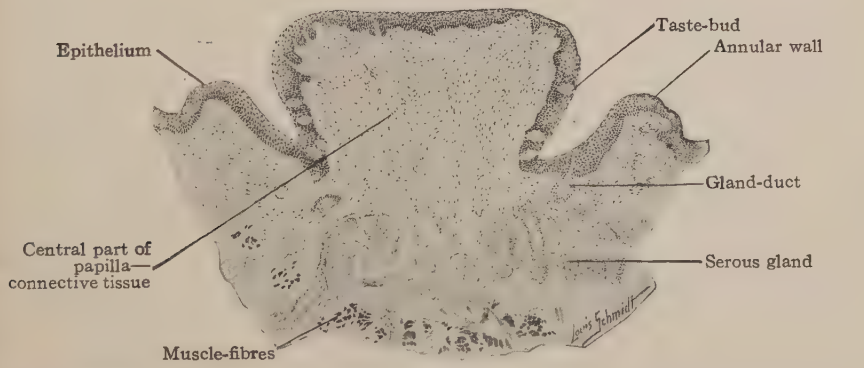


FIG. 189—Section across circumvallate papilla from child's tongue, showing central part and encircling wall. × 45.

tions, from 1–1.5 mm. high and from 2–3.5 mm. broad, consist essentially of a fungiform papilla surrounded by a shallow groove bounded externally by a low annular wall. Their chief interest is their being the principal

seats of the taste-buds which are lodged within the epithelium lining the mesial wall of the groove. Into the bottom of this groove open the ducts of the serous lingual glands. At the edges of the tongue, on each side just in front of the anterior palatine pillar, may be seen a series of small transverse parallel ridges, the **papillæ foliatæ**. This structure, varyingly pronounced in man, but well developed in the rodents, is of interest on account of the many taste-buds which it often contains.

The posterior, or **lymphoid, area,** the part of the dorsum behind the circumvallate papillæ, presents a striking contrast to the anterior two thirds of the mucous membrane. The surface is thrown into irregular rounded elevations which, while smooth and devoid of papillæ, impart to this portion

FIG. 190—Section from posterior third of child's tongue, showing lymphoid tissue constituting a part of lingual tonsil. × 30.

of the tongue an uneven and mammillated appearance that is further accentuated by numerous minute pits. The latter lead into small crypts each lined by stratified epithelium continued from the surface and surrounded by a zone of lymphoid tissue. The latter contains a number of lymph-nodules, with germ-centres blended together by the intervening diffuse lymphoid tissue and lodges in the tunica propria. These spherical masses, the **folliculi linguales,** resemble in miniature the lymphoid organs found on the side-walls of the oro-pharynx and, hence, are often termed collectively the **lingual tonsil.**

The **glands of the tongue** include both mucous and serous varieties, which are distributed in three groups: (1) the serous glands, (2) the mucous glands, and (3) the anterior sero-mucous glands. The **serous glands** are small and occur in the vicinity of the circumvallate and foliate papillæ, occupying the deeper part of the tunica propria, with some alveoli between

the subjacent muscle-bundles. Their ducts lead through the mucosa and open preferably at the bottom of the furrows along which the taste-buds are lodged. They belong to the tubo-alveolar group, with the tubular type of the ultimate compartments pronounced. The gland-cells are somewhat pyramidal, rest upon a basement membrane of great delicacy, and secrete a thin, watery, albuminous fluid. The **mucous glands** are found just in advance of the more median circumvallate papillæ, along the margins of the tongue, and scattered through the lymphoid area, especially towards the root. They are tubo-alveolar in type and are examples of pure mucous glands. Their viscid, mucin-containing secretion is produced by the cylin-

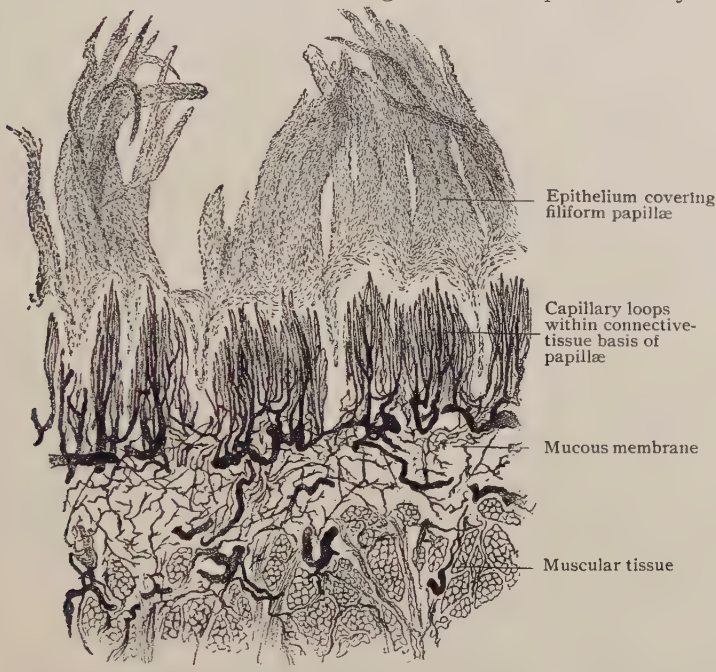


FIG. 191—Injected mucous membrane from upper surface of tongue. × 60.

drical gland-cells and carried off by ducts, which are lined with columnar epithelium and open on the free surface or, not infrequently, into the lymphoid crypts. The **anterior lingual glands,** or **glands of Nuhn,** form two elongated groups, 15–20 mm. long and 7–9 mm. wide, which lie near the tip of the tongue, on either side of the mid-line. Both serous cells and mucous alveoli occur, hence they belong to the mixed mucous and tubo-alveolar type and possess demilunes. They open on the under surface of the tongue.

The **blood-vessels** of the tongue include, in addition to the branches of the lingual artery that break up into capillary networks supplying the muscles, a vascular network within the mucous membrane from which twigs ascend to the papillæ. Each of the latter contains a tuft of elongated capillary loops (Fig. 191), which occupies the connective tissue stroma, including that of the secondary papillæ. Other twigs pass to the glands and

end in capillary networks that surround the alveoli; still others provide capillaries which ramify within the aggregations of lymphoid tissue. The **lymphatics** of the tongue constitute two groups, a superficial within the mucous and submucous layers and a deep one within the musculature. The submucous vessels arise from the rich network of lymph-channels within the dorsal mucosa, the apical network being especially close. The lymph-nodules of the posterior area are surrounded by meshes of lymphatics.

The **nerves** of the tongue include three sets of fibres concerned in conveying the impulses for common sensation, taste, and motion. Those for common sensation, derived from the trigeminus and glossopharyngeal nerves, end in the lingual mucous membrane in the manner already described for the oral mucosa, the papillæ receiving fibres that confer great sensibility. The gustatory impulses are collected by the fibres from the chorda tympani and the glossopharyngeal, which are distributed to the anterior two thirds and the posterior third, respectively. Such fibres end in close relation with the receptive neuro-epithelial cells within the taste-buds. The motor fibres are from the hypoglossal nerve. As in other localities, so here, unmyelinated sympathetic fibres, destined for the blood-vessels, glands, and voluntary muscles, are included in many nerve-trunks along with myelinated fibres.

THE SALIVARY GLANDS

The salivary glands include the **parotid,** the **submaxillary,** and the **sublingual,** all organs of some size, and the elaborate secretions poured into the oral cavity to assist in preparing the food for deglutition and further chemical change. For the latter purpose, the parotid gland is of most importance, and in all animals maintains its character as a true (serous) salivary gland. The others, the submaxillary and sublingual, are variably mixed glands, the former sometimes and the latter never approaching the pure serous type.

The Parotid Gland.—This, the largest of the salivary glands, lies between the upper part of the ramus of the lower jaw, which it overlaps both within and without, and the external ear. It is invested by a strong fibrous **sheath**, continuous with the cervical fascia. The gland is subdivided into many lobules by septa of dense fibro-elastic tissue and, hence, possesses considerable toughness. The parotid consists entirely of serous alveoli, although mucus-producing acini may occur in the **accessory lobules** along the main (Stenson's) duct. The **primary lobules** are made up of alveoli, lined with pyramidal glandular epithelium whose appearance changes with functional activity. When at rest, the cells are filled with minute secretion-granules; the latter, however, are sensitive to reagents, often undergoing partial or complete solution. Hence, the reticulated appearance of the cytoplasm frequently observed in the gland-cells after fixation. The spherical nuclei occupy the middle of the serous cells.

The **duct-system** begins at the alveoli as the intermediate tubules, which in the parotid are relatively long and narrow and lined with low or flattened cells continuous with the alveolar epithelium. Secretion-canaliculi extend between the gland-cells part way to the basement membrane. The intralobular tubules, of larger diameter (35 μ) than either the immediately

preceding or succeeding segments of the duct, are lined with a single layer of columnar cells that exhibit differentiation into an inner zone, finely granular and containing the nucleus and an outer, or basal, zone, next the basement membrane and displaying a faint longitudinal striation or "rods." The interlobular and interlobar ducts gradually increase in diameter and, for the most part, possess a single layer of columnar cells; in the larger canals, however, this may be reinforced by an additional imperfect row of small cells. The columnar cells extend to near the termination of the main excretory duct, where they give place to the stratified squamous epithelium

FIG. 192—Section of small lobule of parotid gland. × 70.

continued into the canal from the oral mucous membrane. The wall of the **parotid,** or *Stenson's*, **duct,** in addition to the epithelium, consists of fibrous tissue, mixed with many elastic fibres and a few bundles of unstriped muscle.

The Submaxillary Gland.—This organ, intermediate in size between the parotid and sublingual glands, lies largely under cover of the lower jaw, invested by a fibrous capsule derived from the cervical fascia. It consists of two parts, the superficial resting on the outer surface of the mylo-hyoid muscle and the deeper, which winds around the posterior border of the last named muscle and extends forwards as a tongue-like process, between the mylo-hyoid and the hyo-glossus muscles almost as far as the sublingual gland, beneath the mucous membrane of the floor of the mouth.

The submaxillary gland differs in structure from the parotid in possessing both serous and mucous alveoli, the mucous forming one fifth or less of the entire gland-tissue. The **alveoli** containing serous cells resemble

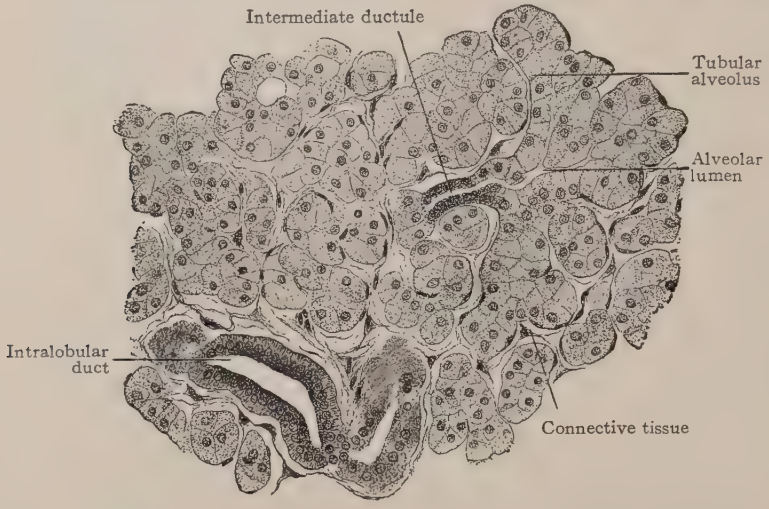


FIG. 193—Section of parotid gland, showing serous alveoli. × 270.

those of the parotid, during rest being filled with cells loaded with minute secretion-granules. These cells often exhibit a differentiation into an inner granular and an outer almost granule-free zone. The mucous alveoli are

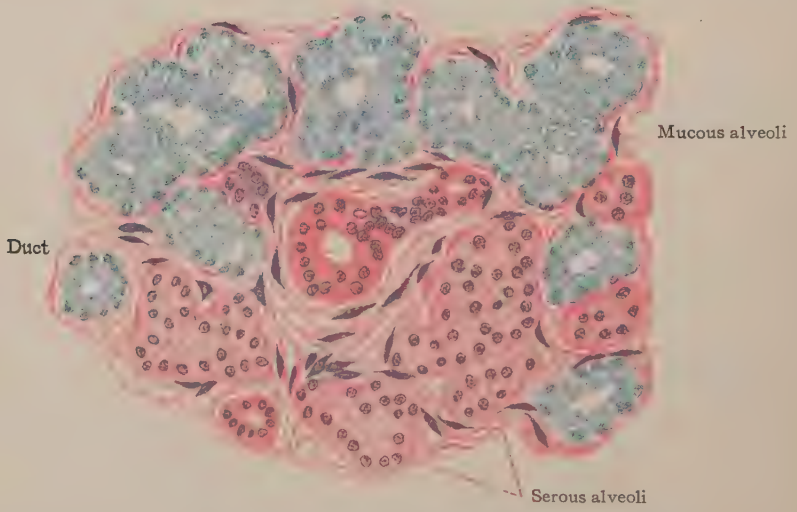


FIG. 194—Section of submaxillary gland, showing serous and mucous alveoli. × 270.

somewhat larger than the serous ones and contain chiefly mucus-secreting cells, although limited groups of serous cells are present as demilunes. Intermediate tubules connect alveoli of both kinds with the intralobular

ducts, those from the mucous alveoli being shorter and less branched than those from the serous. The ductules of the latter are lined with low cells, which pass gradually into the gland-cells of the alveoli, in contrast to the abrupt transition in the tubules leading to the mucous acini. The cells lining the intralobular ducts exhibit the striation seen in the corresponding part of the parotid, this rod-epithelium sometimes containing yellowish pigment. The interlobular and interlobar ducts resemble those of the parotid gland. The main **excretory** or *Wharton's*, **duct** possesses, in addition to its fibrous tissue and a subepithelial layer of elastic fibres, feebly developed bundles of longitudinally disposed unstriped muscle. Goblet-cells appear among the columnar epithelium lining the deeper parts of the duct.

The Sublingual Gland.—This, the smallest of the salivary glands,

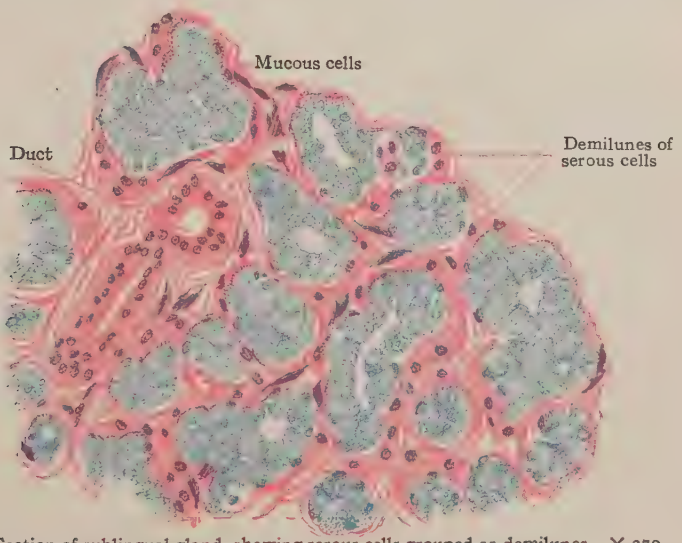


FIG. 195.—Section of sublingual gland, showing serous cells grouped as demilunes. × 270.

underlies the mucous membrane of the floor of the mouth, through which it shows as an oval elevation at the side of the median fold, the frenulum. The gland does not possess a distinct capsule and consists of an aggregation of separate glands, each of which has its independent duct, rather than a consolidated single organ.

The sublingual gland belongs to the mixed mucous type and possesses a curtailed **duct-system,** in which distinctive intralobular ducts and intermediate ductules are wanting. The interlobular ducts subdivide into smaller canals that enter the primary lobules and give off wider passages lined with cuboidal epithelium. Towards the distal ends of these terminal canals the mucous gland-cells appear, at first isolated or in groups, until they constitute the entire lining of the passage. The condition of the **alveoli,** as regards the amount of mucus in the cells, varies even in the same lobule. Sometimes an entire primary lobule is composed of alveoli filled with mucus; at other times empty and engorged alveoli alternate, or the depleted acini may

predominate. The demilunes of serous cells are also uncertain, since these may be absent or present in considerable numbers and of large size. The relatively wide lumen of the alveoli and the more pronounced reticulated appearance of the gland-cells distinguish the exhausted sublingual gland from the parotid under like conditions.

The normal **secretions** of the salivary and oral glands contain no formed elements, although granules and cellular remains may be present. The spherical so-called **salivary corpuscles,** which occur in varying numbers in the mixed oral secretion, have no relation to the salivary glands, since they are only modified lymphocytes which have escaped from the lymphoid tissue of the faucial and lingual tonsils. On entering the mouth, these cells are affected by the saliva and become greatly swollen, the granular remains of their cytoplasm exhibiting molecular motion to a marked degree, as is characteristic of dying protoplasm.

The **blood-vessels** of the salivary and larger oral glands follow the same general arrangement. The larger arteries accompany the ducts in their course within the interlobular connective tissue, giving off twigs which supply the walls of the excretory passages. From the interlobular vessels, branches enter the connective tissue between the primary divisions of the glandular tissue and eventually break up into close capillary networks which surround the individual alveoli, the basement membrane and the endothelium alone separating the blood-stream and the gland-cells. The veins maintain the general path of the arteries. The definite **lymphatics** are limited to the interlobular tissue, usually accompanying the ducts. The **nerves** supplying the salivary glands form plexuses within the interlobular tissue and include both myelinated and unmyelinated fibres. The latter, destined chiefly for the blood-vessels and gland-tissue, are in part the axones of sympathetic neurones, whose cell-bodies are the ganglion-cells collected in microscopic groups along the walls of the larger ducts. On reaching the alveoli, the unmyelinated fibres form epilemmar plexuses on the outer surface of the basement membrane, from which delicate fibrils pierce the membrane to end as varicose hypolemmar threads between the gland-cells.

THE PALATE

The **hard palate** forms the roof of the mouth, and is bounded laterally by the alveolar border of the upper jaw. The mucous membrane is united firmly to the periosteum covering the roof-bones by the dense connective tissue of the submucous layer. Near the front border of the area, the mucous membrane is thrown into a series of irregular ridges, the **palatal rugæ,** over which the secondary papilla of the tunica propria are well marked. On each side of an oval median area, the submucosa is occupied by an almost continuous layer of **palatal glands,** composed of small groups of mucous alveoli, whose ducts open on the surface as minute scattered orifices.

The **soft palate** is essentially a fold of mucous membrane, enclosing muscles, tendinous expansions, and glands, continued backwards and downwards from the hard palate to form the mobile arched partition between

the nasal and oral subdivisions of the pharynx. The free border is prolonged in a median, conical prominence, the **uvula.** The soft palate includes four general layers, which, from above downwards, are: (1) The **pharyngeal mucous membrane,** which for some distance above the free edge of the palate corresponds with the oral mucosa in possessing stratified squamous epithelium and a layer of elastic fibres in the deeper margin of the tunica propria. Higher, but at a variable distance from the free border, the mucosa changes and assumes the characteristics of the respiratory mucous membrane. (2) The **fibro-muscular layer,** which comprises a muscular complex formed chiefly by the expansions of the palatopharyngeus, levator and tensor palati muscles. (3) The **glandular layer,** which is in places 5-6 mm. thick

FIG. 196—Lateral sagittal section of soft palate. × 15.

and continuous with the glands of the hard palate. The glands are examples of the pure mucous variety and so closely set that they form a layer broken only in the mid-line near the hard palate by a fibro-muscular septum. They are continued into the uvula almost to its tip as a tract of mixed glands through and about which run the fibres of the azygos uvulæ muscle. (4) The **oral mucous membrane,** which, although strictly belonging for the most part to the oro-pharynx, resembles the general lining of the mouth. The submucous tissue of this surface contains a variable amount of fat, which is wanting in the corresponding position on the upper aspect of the palate. Scattered small taste-buds are occasionally encountered within the epithelium of the lower surface. The ultimate distribution of the blood-vessels and nerves of the palatine mucosa follows the general plan of the oral mucous membrane.

THE PHARYNX

The pharynx, or throat, is a musculo-fibrous sac, lined with mucous membrane, and extending from the base of the skull to the level of the upper border of the seventh cervical vertebra. It communicates with the Eustachian tubes, the nasal fossæ, the oral cavity, and the larynx, and is continuous below with the œsophagus. The walls of the pharynx comprise three general strata: (1) the **muscular layer,** made up of the striated fibres of the pharyngeal constrictors and the associated muscles; (2) the **fibrous layer,** a membranous framework of dense fibro-elastic tissue, strong above but weaker below and continued into the œsophagus; and (3) the **mucous membrane,** which, with the submucous layer, lines all parts of the pharynx and presents striking local modifications.

FIG. 197—Sagittal section of posterior wall of pharynx child, showing part of pharyngeal tonsil. × 20.

Within the naso-pharynx, that division lying above the level of the soft palate, the mucous membrane mostly resembles that of the adjoining respiratory part of the nasal fossæ, being clothed with stratified ciliated columnar epithelium and containing many small mixed (sero-mucous) tubo-alveolar glands. Over portions of the posterior wall of the naso-pharynx, as well as over the uvula and neighboring region of the upper surface of the soft palate, the epithelium is stratified squamous, the place of transition being subject to great individual variation. The lower divisions of the pharynx, the oro- and the laryngo-pharynx, are invested with stratified squamous epithelium.

Lymphoid tissue occurs in great abundance in certain localities, particularly on the upper posterior pharyngeal wall, causing the mucous membrane to be thrown into elevations. The larger and more constant collections of lymphoid tissue are called "tonsils," of which the **faucial tonsils** in the oro-pharynx, the **pharyngeal tonsil** in the upper part of the naso-pharynx, the **tubal tonsils** at the openings of the Eustachian tubes, and the **lingual tonsil** on the posterior third of the tongue are examples.

The **faucial tonsils,** also called **palatine**, are two almond-shaped masses of lymphoid tissue one on each lateral wall of the oro-pharynx, between the palatine pillars. Each tonsil, some 20 mm. long, 15 mm. broad and 10 mm. thick, is enclosed by a fibrous **capsule,** which becomes continuous with the submucous layer where the mucous membrane is adherent to the tonsil, as it is on the free surface. The latter is broken by an uncertain number (10–20) of pits of varying size and depth. These depressions, or **crypts,** cut the lymphoid tissue into irregular tracts, which are still further subdivided by connective tissue septa that penetrate from the capsule. The crypts, with their side branches, are completely lined in the normal condition with stratified squamous epithelium continued from the adjacent free surface. The tunica propria, however, is thin and so invaded by the lymphocytes that the epithelium is the most conspicuous representative of the mucous membrane. Each crypt with its surrounding tract of lymphoid tissue repeats, in its general makeup, the structure of the lingual lymph-follicle already described. The lymphoid mass contains lymph-nodules, with germ-centres, blended together by the more diffuse lymphoid tissue. The entire tonsil is built up by repetition of such structural units. Numbers of lymphocytes migrate into the subepithelial tissue, which in consequence, becomes infiltrated with the lymph-cells, thence pass into the epithelium and, finally, escape into the pit and onto the free surface of the mucous membrane. These cells become the salivary corpuscles.

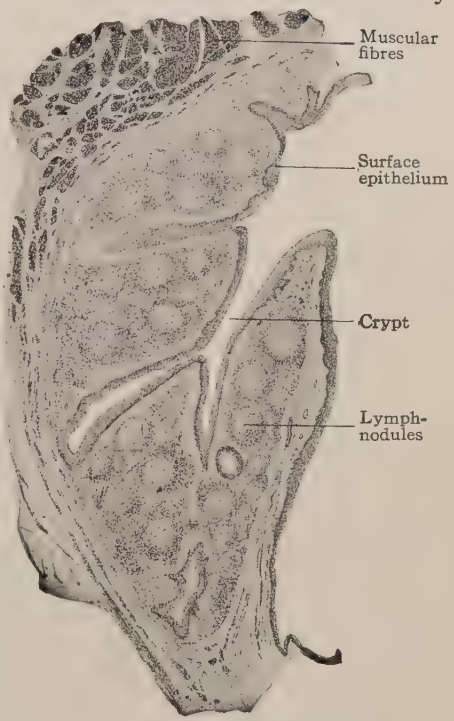


FIG. 198—Section through faucial tonsil, showing general disposition of lymphoid tissue around the crypts. × 20.

The **pharyngeal tonsil** is an unpaired median mass of lymphoid tissue in the postero-superior wall of the naso-pharynx. It, as well as the faucial tonsils, is best developed in early childhood; when hypertrophied, it constitutes "adenoids." This tonsil consists of a series of lobulated masses of lymphoid tissue arranged around a central depression with lateral recesses. In its general composition, it resembles the faucial tonsil, consisting of lymph-nodules and diffuse lymphoid tissue. The latter is less circumscribed and infiltrates the surrounding mucous membrane, so that the limits of the pharyngeal tonsil are not well defined. The name, **tubal tonsils,** is sometimes applied to the collections of lymphoid tissue that surround the openings

of the Eustachian tubes. The lymphoid tract extends for some distance along the tube, as well as towards the pharyngeal tonsil, and contains small lymph-nodules.

The **blood-vessels** and **nerves** of the pharynx, although collectively derived from a varied and somewhat complex source, follow in their detailed distribution the plan common to mucous membranes.

The **lymphatics** within the pharyngeal mucous membrane are unusually abundant, particularly in the vicinity of the more definite masses of lymphoid tissue. The latter, especially the faucial tonsils, are of great practical importance. They are very frequently the seat of serious infections, their numerous and often deep crypts affording favorable resting places for bacteria.

THE OESOPHAGUS

The œsophagus, or gullet, is the tube, about 25 cm. in length, that connects the pharynx and the stomach and serves for the passage of food. Its walls, 3–4 mm. thick, consist of four coats (Fig. 199) which, from within outwards, are: (1) tunica mucosa, (2) tunica submucosa, (3) tunica muscularis, and (4) tunica fibrosa.

The **tunica mucosa,** or *mucous membrane*, usually thrown into longitudinal folds, includes a tunica propria composed of fibrous connective tissue and delicate elastic fibres, and a thick coating of stratified squamous epithelium. The surface of the stroma-layer beneath the epithelium is modelled by longitudinal ridges and papillæ, between which pass the ducts of the glands in their course to the free surface. The deeper part of the tunica propria is occupied by a thin stratum of involuntary muscle, the **muscularis mucosæ,** which is feeble and indistinct in the upper part of the gullet, but robust and conspicuous in the lower portion. Collections of lymphoid tissue occur within the mucosa as more or less distinct aggregations. Mostly they are small diffuse areas around the ducts of the mucous glands, but in some places, especially towards the lower end of the œsophagus, they assume the form of distinct lymph-nodules.

The **tunica submucosa,** or *submucous layer*, although of considerable thickness, is loose in texture and, therefore, permits free motion of the mucous membrane upon the muscular tunic. Scattered along the length of the gullet are many **œsophageal glands.** These are chiefly ordinary *mucous glands*, situated within the submucous coat. They are tubo-alveolar in form and pure mucous in type in man, but in many animals they also contain serous demilunes. The number of glands in the entire human œsophagus varies in different individuals, Goetsch ('10) finding 741, 140, and 62, respectively in three examples examined. Their grouping is also variable, so that in some sections there may be seen several glands, but in other sections none. Their ducts, commonly somewhat tortuous, are often dilated into miniature ampullæ just before penetrating the muscularis mucosæ; they leave the tunica propria and enter the epithelium in the valleys between the papillæ. The smaller ducts are lined with simple columnar epithelium, which in the larger tubes may become stratified and, near the free surface may be replaced by stratified squamous cells. Small aggregations of lymphocytes are often

associated with the glands, usually where the duct leaves the gland and around the duct.

There is also a second set of glands, but infrequently seen, in the tunica mucosa, at the upper end of the œsophagus. They have been termed the superficial œsophageal glands because they are situated superficially to the muscularis mucosæ, in contrast to the usual œsophageal glands. They are formed of branching tubules, the glandular cells taking the mucin stain lightly. They have also been described as **superior cardiac glands,** because

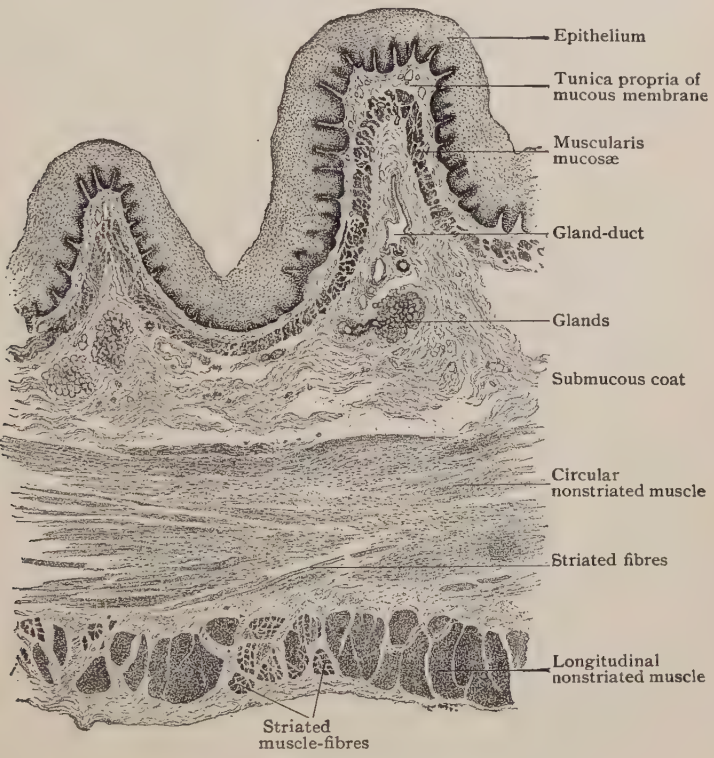


FIG. 199—Transverse section of œsophagus, through middle third. × 18.

of some resemblances to the "cardiac" glands situated in the first part of the stomach adjoining the lower end of the œsophagus.

The **tunica muscularis,** or *muscular coat,* of the œsophagus includes an inner circular and an outer longitudinal layer, although the individual bundles are often irregularly and obliquely disposed, and above somewhat intermingled. The histological character of the muscular tissue varies in different parts of the tube. Thus in a general way, within approximately the lower half of the œsophagus the muscle is entirely unstriped; within the second quarter both striated and unstriped muscle appear; while within the first quarter striated muscle almost exclusively is present. Although within the longitudinal layer unstriped fibres do not appear within the

upper fourth or fifth, the zone of purely striated fibres within the circular layer includes only about the first 2.5 cm., below which level unstriped fibres gradually become more abundant.

The **tunica fibrosa,** or *fibrous coat,* above the diaphragm, consists of areolar tissue that attaches the œsophagus to the surrounding structures, aided in places by strands of unstriped muscle. After piercing the diaphragm, the peritoneum contributes a limited serous coat, which, with its connective tissue stroma and surface mesothelium, constitutes a more definite investment for the alimentary tube on from this point.

The **blood-vessels** of the œsophagus, after sending twigs directly for the supply of the muscular tissue, gain the loose submucous layer, within which lie branches of considerable size. From these, in addition to small vessels for the circular muscle and the glands within the submucosa, twigs are given off that enter the mucous membrane and break up into capillary networks from which terminal loops invade the papillæ. The venous radicles of the mucosa are tributary to the veins within the submucous tissue, from which the larger trunks accompany the arteries.

The **lymphatics** are represented by networks within the submucous and muscular coats. The former take up the fluid from the tissue-spaces of the mucous membrane. These networks are connected by independent trunks with neighboring lymph-nodes, those from the lower end of the œsophagus passing to the upper nodes of the cœliac group.

The **nerves** of the œsophagus include both myelinated and unmyelinated fibres. The former, largely from the vagi, contribute fibres supplying the striated muscle, in which they end in motor plates. The unmyelinated fibres are chiefly sympathetic and, therefore, are destined especially for the involuntary muscle and glands. Between the longitudinal and circular layers of muscle they form a wide-meshed plexus, containing many microscopic ganglia, that corresponds with the **plexus myentericus** of the stomach and intestine, with which organ it will be described. The mucous membrane receives fibres, from an indefinite plexus within the submucous layer, which terminate within the tunica propria in free endings, some threads entering the deeper layers of the epithelium.

THE STOMACH

Being essentially a greatly dilated and modified segment of the digestive tube, connecting the œsophagus and the small intestine, the walls of the stomach agree in their general makeup with those of the other parts of the alimentary canal lying below the diaphragm. They consist, therefore, of four coats—the **mucous,** the **submucous,** the **muscular,** and the **serous.** When moderately distended, the stomach is a somewhat flattened pear-shaped sac, with the large end up and the point bent to the right. The highest part of the stomach is called the **fundus;** the end joining the œsophagus is the **cardia,** and that meeting the intestine the **pylorus.**

The **mucous coat,** or *mucosa,* thickest near the pylorus (1.5-2 mm.) and thinnest at the cardiac end (.35-.55 mm.), is loosely attached to the muscle

by the submucous tissue and, possessing little elasticity, is easily thrown into folds, or **rugæ,** when the other coats contract. During distention these folds are largely effaced, but under the more usual conditions are conspicuous as longitudinal plications, particularly at the pyloric end and along the greater curvature. The surface of the gastric mucous membrane is divided into small, slightly raised, polygonal areas, or **mammillæ.** The latter, from 1-4 mm. in diameter, are stippled with closely placed microscopic pits, the **gastric pits, foveolæ gastricæ,** into which open groups of the individual gland-tubes. The pits are particularly wide (.2 mm.) in the pyloric region, where

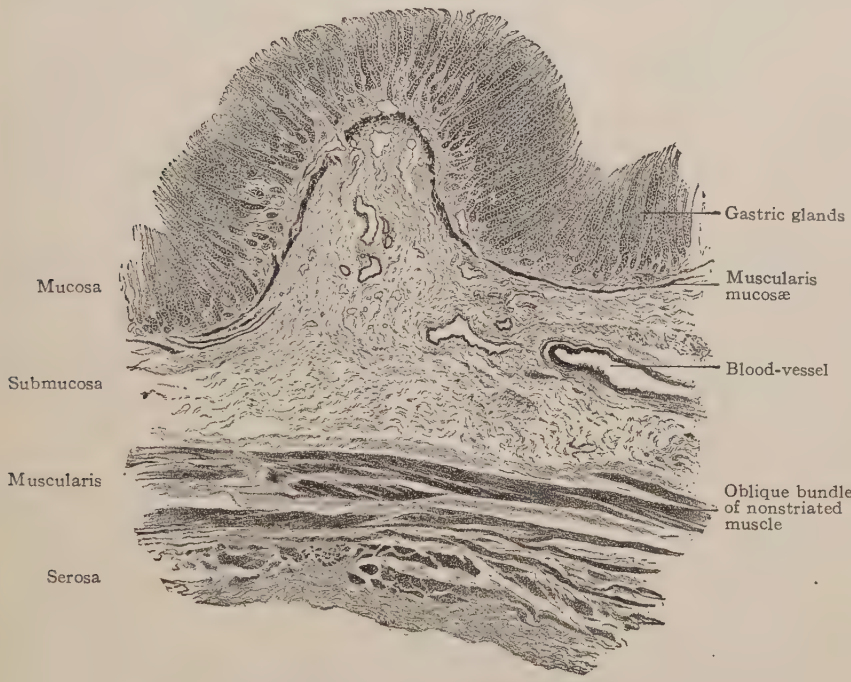


FIG. 200—Transverse section of human stomach, left third, showing general arrangement of coats. × 18.

they reduce the intervening tissue to mere ridges which in section simulate villous projections (**plicæ villosæ**).

The **epithelium** covering the free surface of the mucosa is a single layer of tall columnar cells (20-30 μ high), many of which are engaged in secreting mucus, and consequently appear as goblet-cells. Where the œsophagus joins the stomach, the opaque stratified squamous epithelium of the gullet abruptly changes into the transparent columnar gastric cells. The line of transition is zigzag and well defined, the pale œsophageal mucous membrane contrasting with the reddish-gray gastric lining. The unusual thickness of the mucosa at the pylorus is in part due to the depth of the depressions, the gastric pits, into which the glands open.

The **tunica propria** consists of a delicate connective tissue framework,

composed of fibrous and reticular tissue and elastic fibres, supporting many lymphocytes and intermingled with strands of involuntary muscle and capillaries. This stroma resembles loose lymphoid tissue and, where the gastric glands are closely placed, is reduced to the septa which separate and surround the deeper parts of the gastric glands. The latter, here and there, are so surrounded by aggregations of lymphocytes that the stroma assumes the appearance of lymphoid tissue. In the vicinity of the pylorus and sometimes of the cardia, more definite accumulations of such tissue occur in the form of small **gastric lymph-nodules** (Fig. 203), which are often of lenticular form. Occasionally they are of sufficient size to reach almost the free surface, although commonly they are limited to the deeper parts of the mucous membrane. The **muscularis mucosæ,** as in other parts of the intestinal tube, consists of a thin, but well marked layer of involuntary muscle within the tunica propria next the submucous coat. Two strata are usually distinguishable, an inner circular and an outer longitudinal. Delicate strands of muscle-cells extend between the gastric glands, in places penetrating almost as far as the surface epithelium.

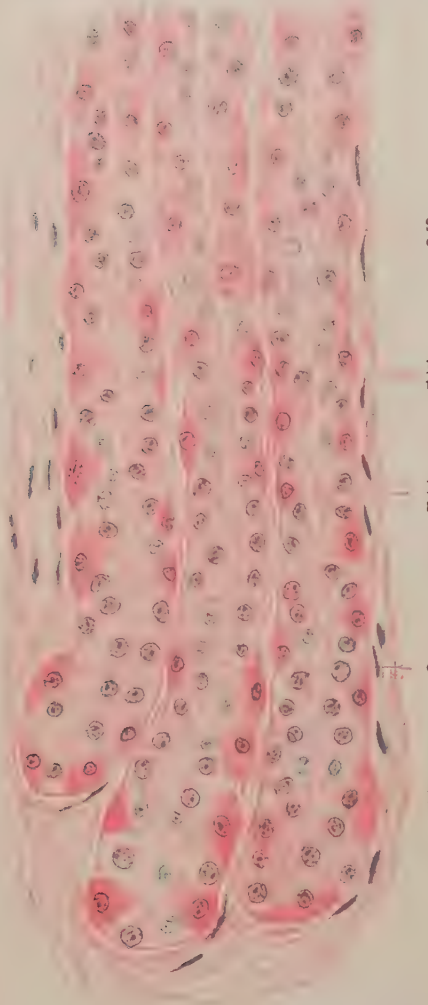


FIG. 201—Deep portions of gastric glands from fundus, showing the two varieties of lining cells and secretion-canaliculi connecting parietal cells with the gland-lumina. × 423.

The **gastric glands** comprise two principal varieties, the **fundus** and **pyloric glands.** The former occur throughout the greater part of the stomach, including the fundus, the anterior and the posterior walls and the curvatures; the latter are limited, in a general way to the pyloric canal. An additional variety, the **cardiac glands,** is represented by a narrow group at the œsophageal orifice, or cardia.

The **gastric glands proper,** or **fundus glands,** are closely set tubules, single or slightly branched and usually somewhat wavy, which extend almost the entire thickness of the mucosa and abut against the muscularis mucosæ. Each gastric pit receives several of the tubules, in which the neck, body, and fundus of the gland are recognized. The slightly constricted neck marks the transition of the columnar epithelium lining the crypt, prolonged from the free surface, into the gland-cells. The latter are of two kinds, the chief and the parietal. The **chief cells,** called also central, or adelomorphous, are clear low cylindrical or cuboidal elements that line the tubule and surround a narrow but distinct lumen. Their spherical nuclei occupy the central part of the clear cytoplasm that sometimes (during rest) is filled with secretion or zymogen granules and at other times, after the granules have disappeared, shows a distinct reticulum. These elements, often imperfectly preserved, are concerned in producing pepsin. The **parietal cells,** known also as acid, oxyntic, or delomorphous, although relatively few are conspicuous by reason of their size, peripheral position (Fig. 201), and selective affinity for certain stains. They take part in the formation of the hydrochloric acid of the gastric juice. They are large, of rounded triangular form, and lie immediately beneath the basement membrane, which often displays in profile an outward bulging as it passes over the cell. The finely granular cytoplasm encloses a distinct spherical nucleus that may be double. Although arranged with little regularity, the parietal cells are most numerous towards the neck of the tubule, where they may form an almost unbroken layer; they decrease in number on approaching the fundus, in which they are few or wanting. When excluded by the chief cells from contact with the lumen of the tubule, the parietal cells are connected with the central cleft by means of lateral channels, the **secretion-canaliculi,** that pass outwards between the chief cells and enclose the parietal cells with networks. In a study of the distribution of the parietal cells, Radasch ('21) finds no gross anatomical landmark, to indicate the boundary between the areas occupied by the fundus and pyloric glands.

The **pyloric glands** differ from the fundus glands in the excessive width and depth of their crypts, the excretory ducts, into which groups of relatively short, tortuous gland-tubules open, and in the character of their lining cells. The latter are almost exclusively columnar or pyramidal elements and their cytoplasm shows a pale mucus reaction. The spherical nuclei commonly lie near the basement membrane. Owing to their tortuous course, the deeper parts of the pyloric tubules, when viewed in sections, are cut in various planes. Within the intermediate zone between the pyloric and adjoining portions of the stomach, the pyloric and the fundus glands are intermingled. Passing towards the intestine, the transition of the pyloric glands into those of the duodenum is gradual, the gastric tubules sinking through the muscularis mucosæ until, as the duodenal glands, they occupy the submucosa.

The **cardiac glands** form a narrow annular group, some 5 mm. in width, surrounding the orifice of the œsophagus. They are poorly developed in man, but are well seen in the junction of œsophagus and stomach in the hog. They are tubular glands which branch several times, and so are easily distinguished from the fundus glands.

The **submucous coat** consists of loose fibro-elastic connective tissue and allows the mucous membrane to move freely on the muscular coat. In the more permanent rugæ, the submucous tissue forms the core of the elevation. The submucosa contains blood-vessels of considerable size, a meshwork of lymphatics and the nerve-plexus of Meissner, as well as occasional groups of fat cells.

The **muscular coat,** composed entirely of unstriped muscle, comprises

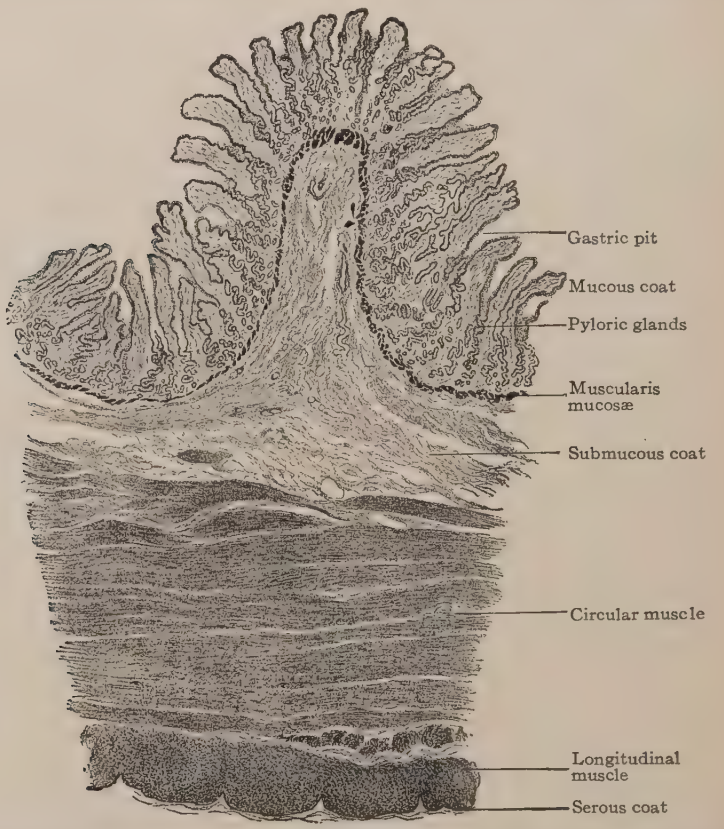


FIG. 202—Transverse section of human stomach, pyloric end; a ruga is cut across, showing the mucosa supported by core of submucous tissue. × 18.

three irregular layers—the external of longitudinal, the middle of circular, and the inner of oblique fibres. None of these layers is complete in all parts of the stomach, the circular being the least imperfect and usually the most conspicuous. The **external layer** consists of longitudinal fibres, continuous with the corresponding ones of the œsophagus above and with those of the duodenum below. It is best developed along the lesser curvature, over the greater curvature and intervening surfaces being a thin and irregular stratum. Towards the pylorus the longitudinal fibres form a more compact and thicker layer, which passes without interruption over the gastro-intestinal

junction into the outer muscle of the duodenum. The **middle layer,** while complete and circularly disposed within the pyloric end, is imperfect and oblique towards the fundus. It is continuous above with the superficial circular fibres of the œsophagus; these, on reaching the stomach, however, are arranged as loops, which overlie the lesser curvature but do not reach the fundus. As these loops pass downward they increase in length and regularity until, at the middle of the stomach, the circular strands completely girdle the organ. Towards the pylorus the circular bundles thicken and, at the immediate end of the stomach, surround the opening into the intestine with a

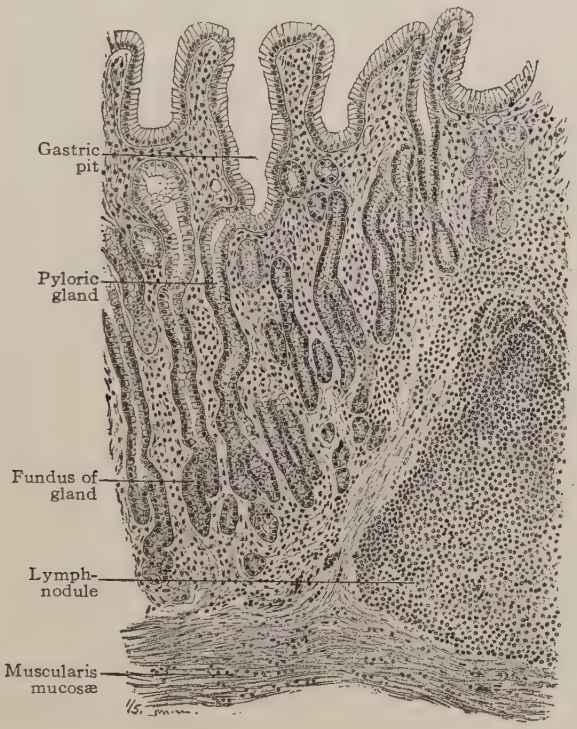


FIG. 203—Section of pyloric end of stomach, showing glands and part of a lymph-nodule. × 80.

robust muscular ring, the **pyloric sphincter,** the outer part of which alone continues into the duodenum. The **inner layer,** the least complete and most oblique, begins at the left of the œsophageal orifice as a prolongation of the deeper circular fibres of the gullet. On the stomach the fibres are disposed as loops which cover the fundus with a fairly continuous layer, but become progressively more oblique and incomplete over the surfaces of the middle third, being absent over the lesser curvature and the pyloric fourth of the stomach. It is evident, therefore, that within the narrow tubular part of the organ, the muscle layers have the most definite and orderly disposition; here they show in cross-sections as a well-developed, inner circular and a definite external longitudinal stratum (Fig. 202).

The **serous coat** corresponds in structure with other portions of the visceral peritoneum, consisting of the surface mesothelial cells and the subjacent fibro-elastic connective tissue.

The **blood-vessels** of the stomach include arterial branches from the three subdivisions of the cœliac artery. At first the arteries lie just beneath the peritoneum, between the fold of which they gain the stomach and to which they give off branches. They then pierce the muscular tunic, whose outer part is supplied during their passage. On reaching the submucous coat the arteries, still of considerable size, form a coarse network, from which some small vessels pass into the muscular layer to complete its supply,

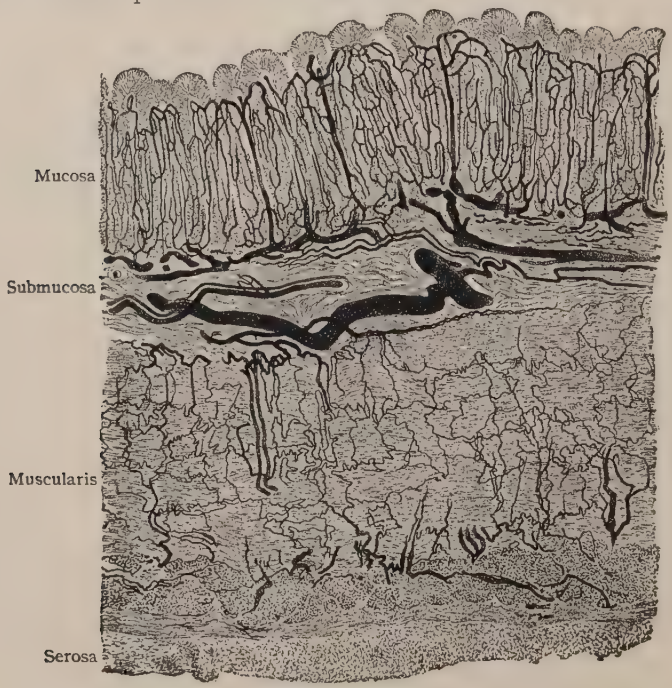


FIG. 204—Transverse section of injected stomach. × 50.

while many more penetrate the muscularis mucosæ and enter the tunica propria. Here they form a network beneath the glands from which pass slender capillaries to surround the gastric tubules and to encircle the mouths of the gastric pits beneath the epithelium. From these superficial capillaries the blood is returned by relatively straight unbranching veins that pass between the gland-tubules and join the venous plexus in the deepest part of the tunica propria. Thence tributaries join the submucous venous plexus from which the larger trunks accompany the arteries. Although the important tributaries of the portal system are devoid of valves, the veins which immediately drain the stomach are provided with such folds.

The **lymphatics** of the stomach begin within the tunica propria as blind capillaries that course between the gland-tubules as far as the close network

in the depth of the stroma. Numerous channels establish communication between the lymph-paths of the mucosa and the wide-meshed plexus of larger vessels within the submucous coat. A second network of lymph-capillaries extends between the layers of muscle and joins the efferent lymph-paths that connect the gastric walls with the neighboring nodes.

The **nerves** of the stomach are from the vagi and the sympathetic and contain both myelinated and unmyelinated fibres, the latter predominating. After forming a **subserous plexus** beneath the peritoneum, they pierce the external layer of longitudinal muscle and between the latter and the circular muscle broaden out and unite into the **plexus myentericus,** or **plexus of Auerbach.** This is an extended network, with rounded angular meshes, whose points of intersection are occupied by microscopic ganglia composed of small groups of sympathetic cells. From these numerous fibres pass to the adjoining sheets of involuntary muscle to terminate in free endings among the fibre-cells. Other fibres form the intramuscular plexus and penetrate, as obliquely directed bundles, the intervening muscle to gain the submucous coat. Within the latter they form the **submucous plexus,** or **plexus of Meissner,** which, while resembling the intramuscular network in its general features, is less pronounced, finer meshed and beset with smaller ganglia. Numerous unmyelinated fibres leave the submucous plexus to enter the overlying tunica propria, in which some end in delicate plexiform threads around the gastric glands and others in fibrils for the muscularis mucosæ. Myelinated fibres, dendrites of sensory neurones, are also present within the mucosa, where they form a subepithelial plexus after losing their myelin sheath. They end in minute varicose threads within the tunica propria; whether some fibrils pass between the epithelial cells is uncertain.

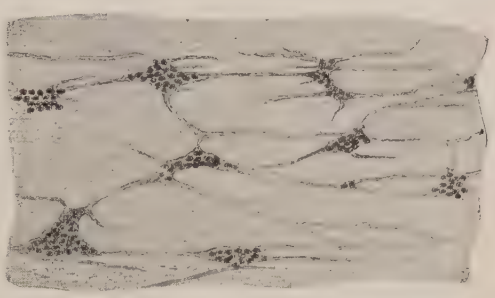


FIG. 205—Surface view of muscular coat of stomach, showing groups of ganglion-cells and nerve-fibres of plexus of Auerbach. × 50.

THE SMALL INTESTINE

The small intestine, about 7 meters or 23 feet in length, is conventionally divided into three parts—the **duodenum,** the **jejunum,** and the **ileum**. Although typical portions of these segments can be readily distinguished from one another, chiefly by the modifications of the mucous coat, the transition between them is so gradual that differentiation in places is impossible. The small intestine, as other parts of the alimentary tube below the diaphragm, consists of four coats—the **mucous,** the **submucous,** the **muscular,** and the **serous.**

The **mucous coat,** or *mucosa,* presents the greatest variations, since its function as an absorbent surface requires an extent of area most economically provided by folds and projections. These elevations of the

mucosa, which include plications and villi, are most marked in the upper part of the intestine, where absorption is most active, thence gradually decreasing until in the terminal part, where the small intestine passes into the large, they almost disappear.

The **epithelium,** everywhere covering the free surface, including the villi, consists of a single layer of columnar cells, whose ends next the intestinal lumen are invested by a narrow and often delicately striated cuticular

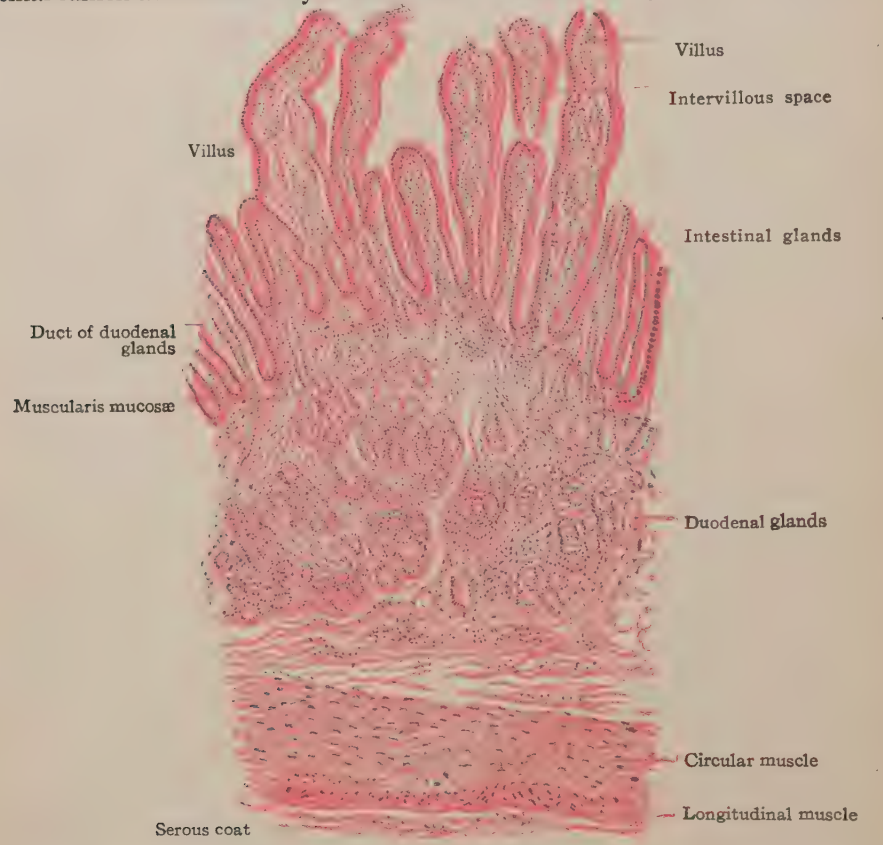


FIG. 206—Transverse section of small intestine (duodenum), showing general arrangement of coats and the two varieties of glands. × 90.

border. These are the absorptive elements through which all the products of digestion pass in order to enter the circulatory systems. During the processes of digestion, their cytoplasm is often loaded with particles of fat, which are readily demonstrable. Their oval nuclei occupy the basal parts of the cells. Other nuclei, each surrounded by a light zone of cytoplasm, belong to migratory lymphocytes, usually seen between the epithelial cells. In places, especially over the villi, many of the epithelial elements are engaged in producing mucus and hence, appear as goblet-cells. The **tunica propria** of the intestinal mucosa resembles lymphoid tissue, since it consists of a

delicate connective tissue reticulum containing numerous small round cells similar to lymphocytes. This stroma fills the spaces between the glands and forms the core of the villi over which the epithelium stretches. The deeper part of the mucosa is occupied by a well-marked **muscularis mucosæ,** composed of an inner circular and outer longitudinal layer of unstriped muscle.

The **villi** are minute projections of the mucosa, barely visible to the un-

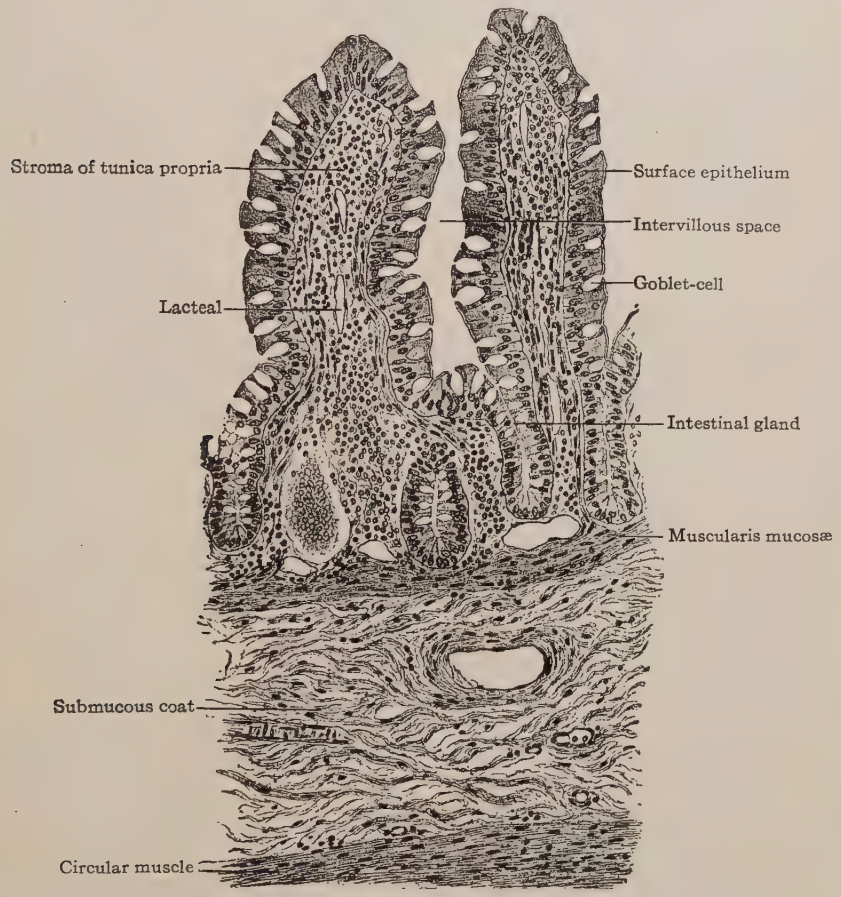


FIG. 207—Transverse section of small intestine (jejunum), showing the villi cut lengthwise. × 150.

aided eye, whose presence imparts the characteristic velvety appearance to the inner surface of the small intestine. Although found throughout the latter (but absent in the large intestine), they are most abundant (20–40 to the sq. mm.) in the duodenum and the jejunum and less numerous (15–30 to the sq. mm.) in the ileum. In the duodenum they appear close to the pylorus, but are better developed in the second part, where they are low and broad and measure .2–.5 mm. in height and .3–1 mm. in width. In the jejunum the villi are conical and somewhat laterally compressed, while in the ileum their

shape is cylindrical, filiform, or wedge-like and their height from .5–1 mm. The villi are projections of the mucous coat alone (Fig. 207) and consist of a framework of the lymphoid stroma-tissue, covered by epithelium, supporting the absorbent lymph- and blood-vessels and intermingled with a few strands of unstriped muscle. The supporting framework of the villus—a complex of fibrous, reticular, and elastic tissue—is condensed beneath the epithelium into a delicate membrane. The **lacteal,** as the absorbent lymphatic vessel within the villus is usually termed, begins as a blind, often slightly club-shaped, channel which runs through the centre of the villus, surrounded by the delicate muscle-bundles and the blood-capillaries. While the slender cylindrical villi possess a single lacteal (25-35 μ in diameter), those of broader form often contain two, three, or even more such vessels, which may communicate by cross-channels. Their walls consist of a single

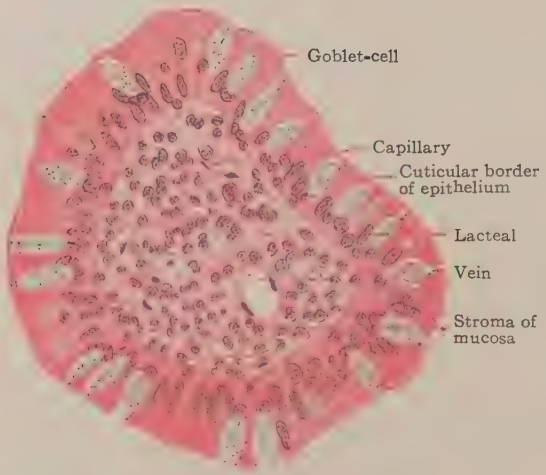


FIG. 208—Transverse section of a single villus, showing relation of epithelium, stroma and vessels. × 350.

layer of endothelial cells and are surrounded by the strands of muscle. While the absorbent vessels within the villi are at times conspicuous by reason of the particles of fat which they contain, and hence are called "lacteals," they are only blind lymph-radicles and actually belong to the system of lymphatics. Their special purpose is to carry the materials taken from the intestinal contents to the great lymph-channel, the thoracic duct.

The **circular folds** (*plicæ circulares*, or *valvulæ conniventes*) within the duodenum and jejunum additionally model the mucous membrane and greatly increase its secreting and absorbing surface, as well as retard the passage of the intestinal contents, thereby facilitating the digestive processes. These transverse folds begin in the second part of the duodenum and are duplicatures which involve not only the entire thickness of the mucosa, but contain a central supporting projection of the submucous coat (Fig. 209), hence they can not be completely effaced by distention. The height of the folds where well developed, rarely exceeds 6 mm., and towards the lower

part of the jejunum is much less; in the terminal portion of the ileum they usually are wanting.

Glands.—The glandular structures within the wall of the intestinal tube include two groups, the duodenal glands of Brunner and the intestinal glands, or crypts of Lieberkühn.

The **duodenal glands** or *glands of Brunner*, (Fig. 210) are limited to the first division of the small intestine. Beginning at the pylorus, where they are most numerous and extensive, they gradually decrease in number and size untii, at the lower end of the duodenum, they are entirely wanting. In the vicinity of the opening of the bile-duct, however, they are locally augmented. These glands are apparently direct continuations of the pyloric glands of the stomach which at the pylorus penetrate the muscularis mucosæ and so come

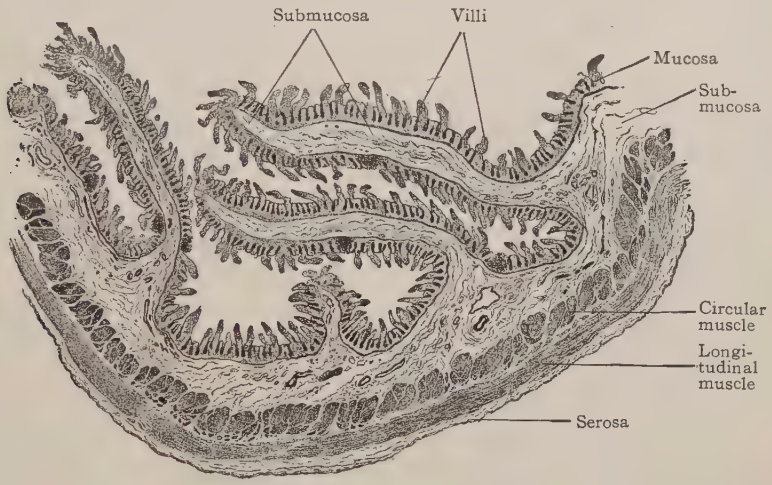


FIG. 209—Longitudinal section of duodenum; plicæ circulares are cut across, showing relation of these folds to the villi. × 11.

to lie within the submucous coat of the duodenum. (Fig. 211). The upper part of the duodenum possesses, therefore, a double layer of true glands—the crypts of Lieberkühn within the mucous coat beneath which, in the submucosa, lie the glands of Brunner. The individual duodenal glands, tubo-alveolar mucous in type, form somewhat flattened spherical or polygonal masses (.5-2 mm.) consisting of richly branched tubules ending in dilatations. Their excretory ducts pierce the muscularis mucosæ and, after traversing the tunica propria, open directly on the free surface between the crypts of Lieberkühn.

The **intestinal glands,** or *crypts of Lieberkühn*, are simple tubular depressions which are found not only throughout the small intestine, but the large one as well. Under low magnification, the surface of the small intestine exhibits numerous minute depressions, the orifices of these crypts, which almost fill the spaces between the bases of the villi; with the exception of the areas immediately overlying the lymph-nodules, where they are displaced,

these glands are present in all parts of the intestinal tube. They are very closely set, narrow and penetrate the tunica propria as far as the muscularis mucosæ. In length they vary from .2-.4 mm., and in diameter from 60-80 μ.

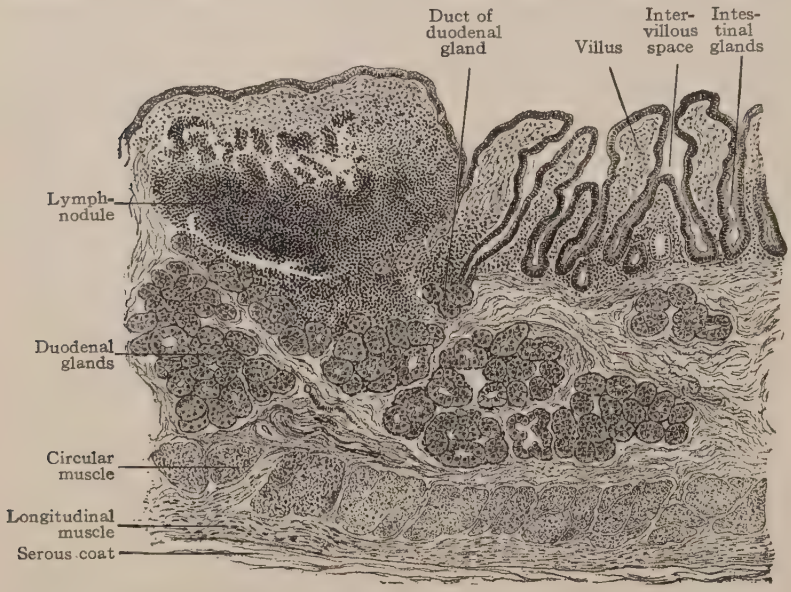


FIG. 210—Longitudinal section of duodenum, showing duodenal and intestinal glands, villi and lymph-nodule. × 68.

The wall of the crypts consists of a single layer of columnar cells resting upon a delicate basement membrane. The cells are continuous with those covering the villi, but differ from these in being shorter and without the cuticular

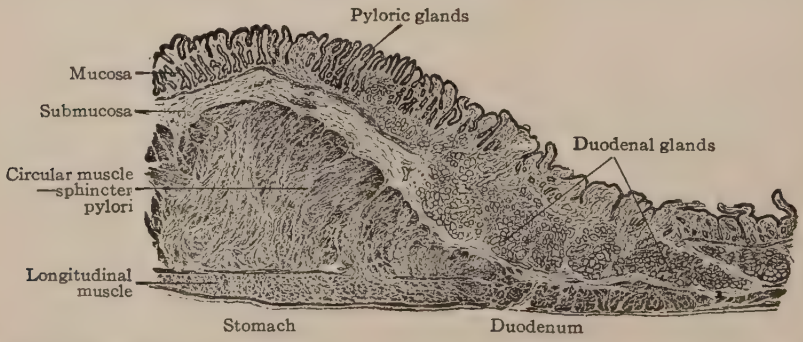


FIG. 211—Longitudinal section through junction of stomach and duodenum, showing transition of pyloric into duodenal glands; also thickening of circular muscle to form sphincter pylori. × 15.

border seen on the villi. In view of the presence of mitotic figures within the crypt-epithelium of the adult, it is probable that the young cells here produced are gradually pushed upwards and supply the elements required to replace the old worn-out surface cells on the villi. Goblet-cells, as well as

migratory blood-corpuscles, occur among the lining of the crypts. Constantly within the human ileum, the deepest parts of the crypts of Lieberkühn contain small groups of granular elements, the **cells of Paneth,** whose significance is undetermined. The duodenum, jejunum, and vermiform appendix are uncertain seats of these cells, while within the large intestine they are absent. The fact that such cells are wanting in many orders of animals possessing well developed intestinal crypts points to some special, rather than a general, purpose.

Lymph-Nodules.—The lymphoid tissue within the intestinal tube occurs in the form of circumscribed nodules, which may remain isolated, as the solitary nodules, or be collected into considerable masses, as the aggregated lymph-nodules of Peyer.

The **solitary nodules** vary greatly in number and size, sometimes being abundant in all parts of the small intestine, at other times almost wanting; usually they are few in the upper and numerous in the middle and lower parts of the tube. They appear in the tunica mucosa as small whitish elevations, spherical or pyriform in shape and from .2-2.5 mm. in diameter. Villi and intestinal glands are wanting over the prominence of the nodules (Fig. 213).

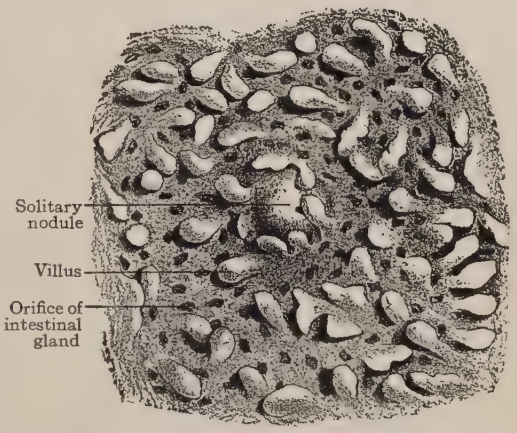


FIG. 212—Surface view of mucous membrane of small intestine (ileum), showing villi, glands, and solitary lymph-nodules. × 10.

In structure the solitary nodules correspond to lymph-nodules in other localities, consisting of a delicate reticulum which supports the lymphocytes within its meshes. Within the larger nodules, spherical or ellipsoidal germ-centres are present; as a rule in young subjects, but often absent in older ones. Each nodule is surrounded by a rich network of small blood-vessels, from which fine capillaries penetrate the lymphoid mass (Fig. 157). Definite lymph-paths are absent within the nodules, although a plexus of lymphatics surrounds their exterior. When the solitary nodules are very large, they press into the submucosa, otherwise they are confined to the mucosa.

The **aggregated nodules,** or *Peyer's patches*, are collections of simple nodules, the individual nodules being connected by intervening lymphoid tissue (Fig. 213). They are present in the lower half of the small intestine, especially in the ileum, but exceptionally are found as high as the beginning of the jejunum. The patches appear as slightly raised elongated oval areas. They usually number about thirty, although as few as eighteen and as many as eighty have been counted. Their length is ordinarily from 1-4 cm. and their breadth from 6-16 mm. Each patch contains from 20-30 ovoid

individual lymph-nodules which, when well developed, occupy both the mucous and submucous coats, their smaller ends almost reaching the epithelium and their bases the muscular tunic. The villi and glands are absent over the nodules, but are sparingly present between the nodules, always being less developed here than beyond the boundaries of the lymphoid area. In structure, the component lymph-nodules correspond to the solitary nodules, the aggregated nodules being blended into a continuous mass by the less dense lymphoid tissue filling the spaces between the individual nodules. The entire patch is defined from the surrounding tissues by an imperfect fibrous capsule.

The **submucous coat** of the small intestine, although lax, does not allow displacement of the plicæ circulares, except in the lower part of the tube. In

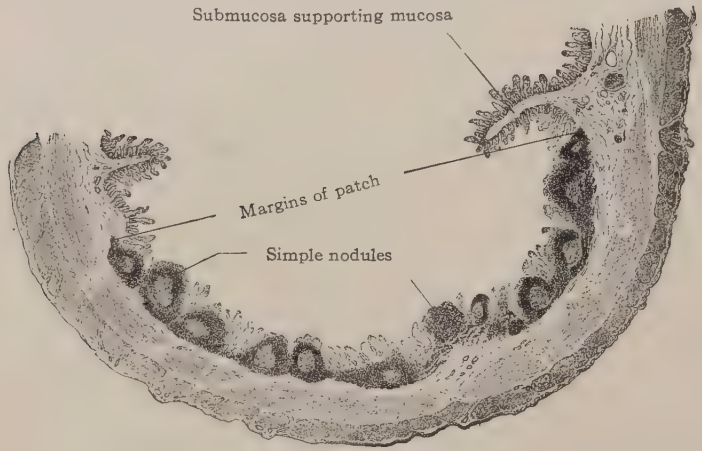


FIG. 213—Transverse section of ileum, showing a Peyer's patch cut across. ×8.

addition to Brunner's glands, the submucosa contains blood-vessels and lymphatics of considerable size, and the nerve-plexus of Meissner.

The **muscular coat,** about .4 mm. thick, consists of an inner circular and an outer longitudinal layer of involuntary muscle. The circular stratum is some two or three times as thick as the longitudinal one and is the more regular in arrangement. The thin longitudinal layer is often imperfect, especially along the attachment of the mesentery. The entire muscular coat diminishes in thickness towards the lower end of the small intestine.

The **serous coat,** with the exception of parts of the duodenum, completely invests the gut except along the line of attachment of the mesentery, where the two layers of peritoneum diverge, leaving a non-serous area between them for the passage of blood-vessels, lymphatics, and nerves. In structure the serous coat of the intestine corresponds to that of the stomach, and includes essentially the fibro-elastic connective tissue stroma, covered on the free surface with mesothelium.

The **blood-vessels** supplying the small intestine reach the walls of the tube between the peritoneal folds constituting the mesentery. After sending

branches to the serous coat, the arteries penetrate the muscular tunic (to the outer part of which twigs are given in passing) to gain the submucosa. Within the latter, additional twigs are given to the muscular coat, while others supply the glands and lymph-nodules lying in this tunic. Larger branches pass from the vessels of the submucosa into the mucous membrane, some to break up into capillaries forming networks around the gland-tubules and others to supply the villi. Each villus receives from one to three arterioles, which resolve into capillaries occupying the peripheral part of the stroma immediately beneath the epithelium. The blood is returned by a single axial vein which becomes tributary to the larger venous stems within the submucous coat, as do the other veins of the tunica propria. The veins within the submucosa accompany the arteries through the muscular coat and unite into the emergent venous channels that course with the arteries between the peritoneal folds.

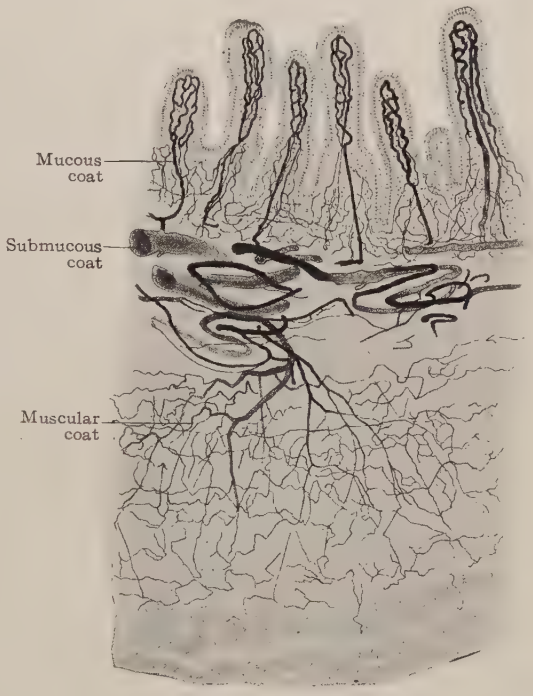


FIG. 214—Transverse section of injected small intestine, showing general distribution of vessels. × 45.

The **lymphatics** of the small intestine, long known as the **lacteals** on account of their milky appearance when containing finely divided globules of fat, begin as the absorbent vessels of the villi. In addition, lymph-channels form a plexus within the tunica propria in the neighborhood of the muscularis mucosæ, from which tributaries pass to the larger submucous plexus. The latter is characterized by irregular contours, due to the dilatations associated with the numerous valves. The emergent lymphatics penetrate the muscular coat and, within the serous tunic, unite into larger trunks that pass to the lymph-nodes between the peritoneal folds; from these smaller nodes lymphatics converge to the larger mesenteric lymph-nodes.

The **nerves** supplying the small intestine are derived from the solar plexus, and include both myelinated and unmyelinated fibres, the latter being chiefly from the sympathetic. In their distribution, they closely follow the arrangement observed in the stomach, including the plexus of Auerbach and of Meissner and, additionally, a plexus of unmyelinated fibres within the villi.

THE LARGE INTESTINE

The large intestine, subdivided into the cæcum, the colon, and the rectum, measures about 1.6 meters or about 5 feet in length. As other parts of the intestinal tube, it consists of four coats—the mucous, submucous, muscular, and serous.

The **mucous coat** of the large intestine agrees in its essential structure with that of the small intestine, consisting of a **tunica propria,** resembling lymphoid tissue, covered by a single layer of columnar **epithelium** exhibiting a cuticular border. It differs, however in having neither villi nor plicæ cir-

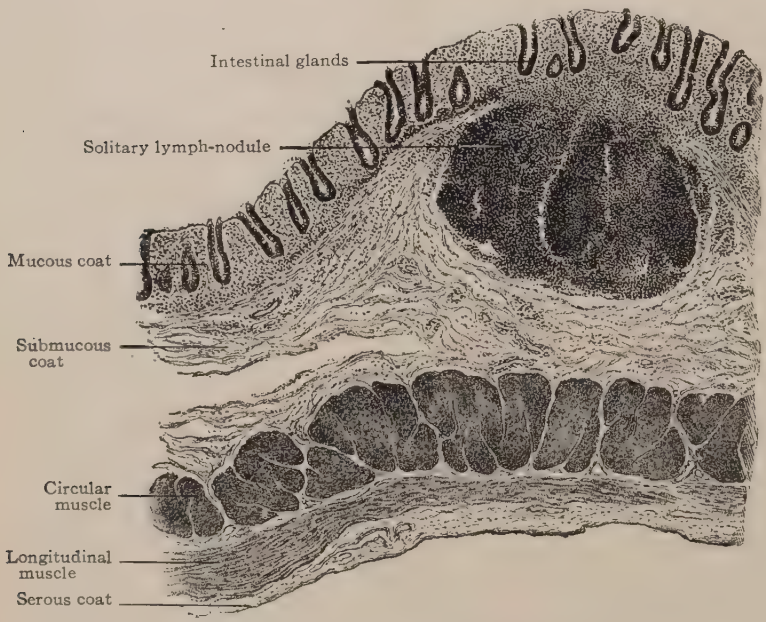


FIG. 215—Longitudinal section of large intestine (ascending colon), showing the general arrangement of the coats and a solitary lymph-nodule. × 30.

culares, and in consequence, lacks the velvety appearance of the small intestine, the mucous surface being smooth, although thrown into folds and pouches by modifications in other coats. The muscularis mucosæ is less regular in its development, being feebly represented in the colon and exceptionally thick in the rectum.

The **intestinal glands,** or *crypts of Lieberkühn,* resemble those of the small intestine, but are larger (.4–.5 mm. long) and less interrupted. Within the rectum they may attain a length of .7 mm. The lining of the crypts is conspicuous on account of the abundance of goblet-cells, which in the middle and upper part of the tubules almost replace the ordinary epithelial elements. As in the small intestine so here, mitotic figures are often seen in the cells lining the crypts, the new elements so arising being eventually pushed to the surface to replace the old ones that are disappearing.

The **lymphoid tissue** occurs as solitary nodules only, aggregated nodules being absent in the large intestine. The solitary lymph-nodules are largest and most plentiful in the cæcum and in the vermiform appendix, in the latter situation they are especially numerous and placed at short intervals apart. In the colon the nodules are less abundant, but in the rectum they are again numerous. They are generally of larger size (1.5–3 mm.) than in the small intestine.

The **submucous coat** closely resembles the similar fibro-elastic connective tissue tunic of the small intestine, and allows fairly free play of the mucous membrane. In addition to the blood-vessels, lymphatics, and nerve-plexus of Meissner, it contains the deeper and more expanded portions of the solitary lymph-nodules.

The **muscular coat** includes a thicker internal layer of circular fibres

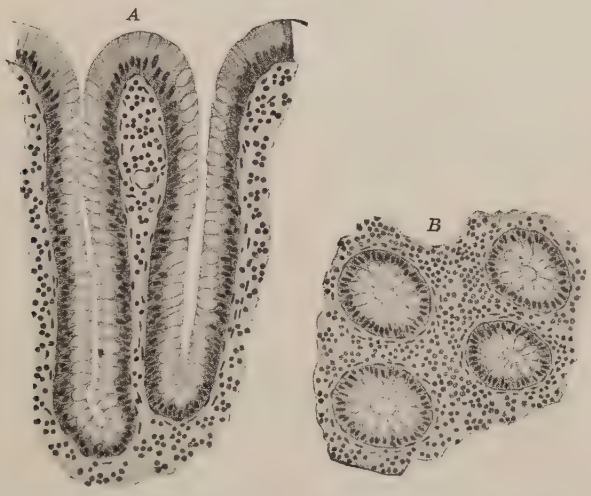


FIG. 216—Portion of mucosa of large intestine, showing crypts of Lieberkühn cut lengthwise (*A*) and crosswise (*B*); epithelial elements contain mucus and are "goblet-cells." × 160.

and an external one of longitudinal fibres; the latter, however, are not uniformly distributed, but, in most places, are collected into three bands, the **tæniæ,** between which the longitudinal muscular coat is extremely thin or imperfect. These bands are shorter than the layers of the intestinal wall internal to them, and are responsible for the characteristic sacculation of the large intestine. The circular muscle increases markedly towards the lower end of the rectum, and in the anal canal becomes augmented into a sheet of involuntary muscle, some 4 mm. thick, known as the **internal sphincter.**

The **serous coat** is incomplete in certain parts of the large intestine owing to secondary changes during development and growth. In structure it corresponds to the peritoneal investment of other parts of the alimentary tract. The characteristic little fringes, or bags, the **appendices epiploicæ** that are attached particularly along the median aspects of the ascending

and decending colon and on the lower side of the transverse colon, consist of pouches of peritoneum filled with adipose tissue.

The blood-vessels, lymphatics, and nerves of the large intestine follow, in the details of their distribution, the general plan described in connection with the small intestine.

The **ileo-colic valve,** guarding the entrance of the ileum into the large intestine, results from the thrusting of the small gut into the large during fetal life, in such a way that ordinarily all layers of the intestinal wall are involved. Where the two serous coats come into contact, the mesothelium disappears and the permanent union is effected by the fibro-elastic connective tissue. Although both layers of the original muscular coat are carried into the folds of the valve, it is the circular muscle that undergoes marked thickening and forms the efficient sphincter guarding the opening. The mucosæ covering the two sides of the crescentic valve-folds differ, that continued from the ileum possessing villi which, as rudimentary elevations, continue almost to the margins of the folds.

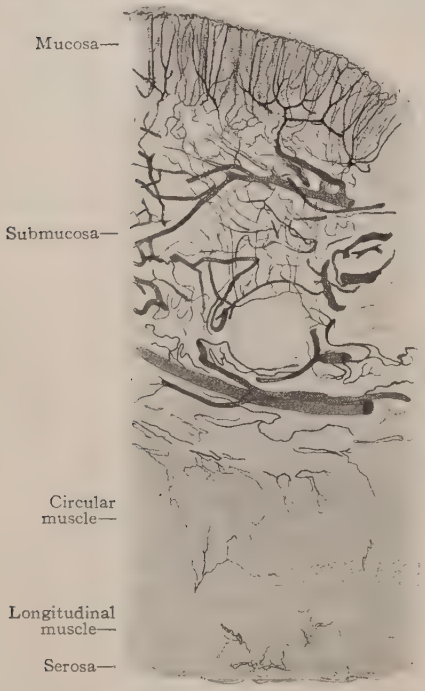


FIG. 217—Transverse section of injected large intestine, showing distribution of arteries to the coats. × 20.

The **vermiform appendix,** the slender worm-like appendage attached to the cæcum, about 8.4 cm. (3¼ in.) long and 6 mm. in diameter, contains all the coats of the large intestine. The mucous coat is thrown into longitudinal folds and encloses a narrow irregular lumen. In its general structure it corresponds to the mucosa of the large intestine, but is infiltrated to an unusual degree with lymphocytes. These are collected into many solitary lymph-nodules, the lymphoid tissue being so abundant that in the ordinary autopsy specimen it often almost encircles the appendix as a continuous mass. In the normal appendix, however, the nodules remain as discrete masses. The intestinal glands contain an unusually large number of goblet-cells; these are, however, few on the free surface. The inner circular muscle is about twice as thick as the external longitudinal layer. The lymphoid tissue of the vermiform appendix is, as elsewhere, most developed in childhood and tends to atrophy in middle life. Along with such atrophy, the walls of the appendix manifest a disposition to adhere, more or less obliterating the lumen of the tube. In consequence of these changes, after the thirty-fifth year the appendix often exhibits variations from the normal condition.

The **rectum,** including the anal canal, presents certain modifications. The intestinal glands are especially large (.7 mm. in length), although less

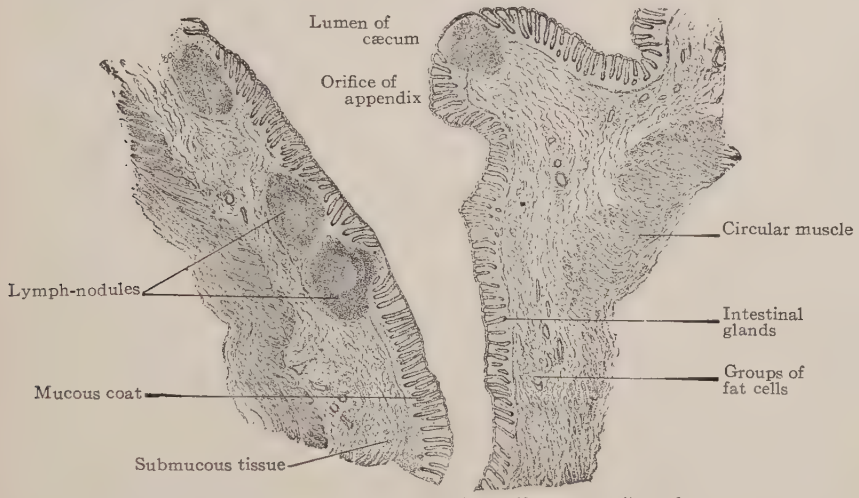


FIG. 218—Longitudinal section through junction of vermiform appendix and cæcum. × 10.

numerous, and do not entirely disappear until the transition of the columnar to the stratified squamous epithelium has been reached or, sometimes, even

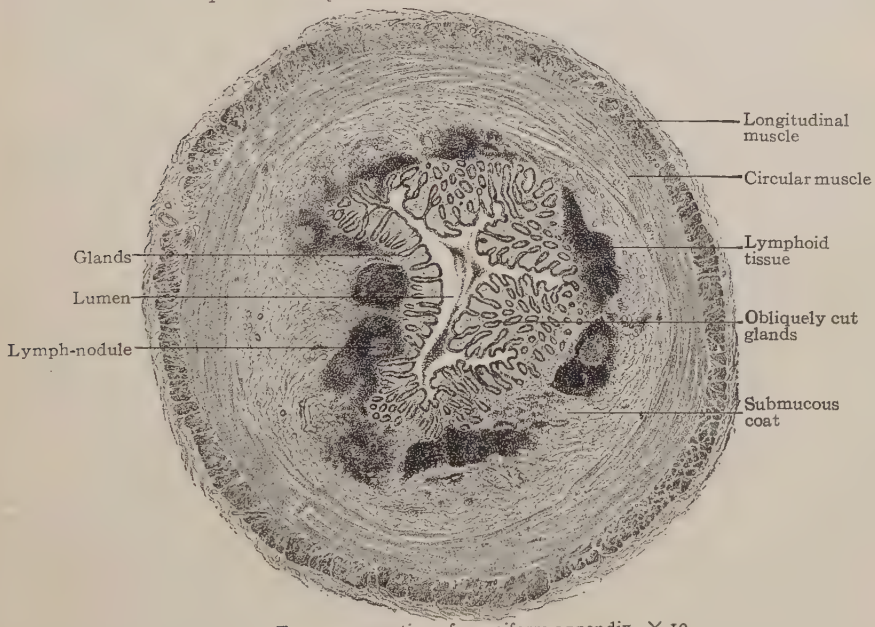


FIG. 219—Transverse section of vermiform appendix. × 10.

slightly passed. This transformation begins at the upper ends of the vertical mucosa-folds, the **rectal columns** or columns of Morgagni, that surround the anal canal and contain strands of muscle; at the level of the crescentic folds

the **anal valves,** connecting the bases of the columns, the mucous membrane is replaced by the skin lining the lower segment of the anal canal. The surface of the rectal mucosa is punctated with minute tubular depressions, the **rectal pits** of Cunningham, at the bottom of each of which is an accumulation of lymphoid tissue resembling a lymph-nodule. The submucous coat is lax and contains the extensive hemorrhoidal plexus of veins. In addition to the temporary folds, the rectal mucous membrane presents usually three crescentic shelf-like projections, the **rectal valves,** that are ineffaceable. These plicæ are formed by the infolding of the mucosa, submucosa, and greater part of the muscular tunic, a portion of the longitudinal muscle passing over the creases externally. The shortness of the muscular bands, into which the longitudinal muscle is condensed in front and behind, serves to maintain these transverse folds. Where the peritoneum is wanting, as it is except over part of the anterior aspect of the rectum, the serous coat is replaced by a fibrous one composed of fibro-elastic tissue.

THE PERITONEUM

The peritoneum, the serous membrane lining the abdominal cavity and covering more or less completely the therein contained organs, consists of a connective tissue **stroma** and the surface layer of **mesothelium.** The latter is a single layer of plate-like cells (Fig. 27) irregularly polygonal in outline and of varying size, whose contours are mapped out, after staining with silver nitrate, by delicate sinuous dark lines that correspond with the particles of reduced silver in the intercellular cement-substance. Each cell encloses an oval flattened nucleus, usually somewhat eccentrically placed. The size and form of the mesothelial plates vary much with the tension to which they are subjected; when unduly stretched, they are often imperfect or, indeed, displaced.

The **stroma** consists of a feltwork of connective tissue bundles of variable fineness, those of the parietal being commonly more robust than those of the visceral peritoneum. The deeper part of the stroma contains numerous elastic fibres, which are most abundant and developed in the parietal sheet, where they form a distinct network. Seldom in the mesenteries but constantly in the omenta, the stroma undergoes a rearrangement whereby larger or smaller openings, **fenestra,** result (Fig. 43). In this manner what originally was a continuous sheet becomes a fenestrated membrane, over which the mesothelium stretches as an unbroken covering, investing the trabeculæ as well as the parts still retaining the character of membranes. The nuclei of the connective tissue cells and those of the mesothelial plates are seen intermingled. Although all the important peritoneal folds, as the mesenteries, omenta, and many of the so-called ligaments of the viscera, theoretically include two layers of serous membrane prolonged from the body-wall, in which course the vessels and nerves supplying the organs, such duplicatures fuse and so come to consist essentially of a general connective tissue stroma-layer covered on each side by a layer of mesothelium. Wherever two peritoneal surfaces are brought into permanent contact, the mesothelium

disappears and the serous character of the attachment is lost, the union henceforth being one of fibrous tissue. Where readily movable, as over most parts of the abdominal and pelvic walls and many folds, the attachment of the peritoneum to the subjacent parts is effected by a layer of fat-laded **subserous tissue.** This fibro-elastic layer varies in thickness, but in many places, as over the liver, stomach, and intestine, where the peritoneum is intimately attached, the subserous tissue is so reduced as to be practically wanting. In certain localities, conspicuously in the broad ligament of the pelvis, the subserous tissue contains strands of unstriped muscle.

The **blood-vessels** supplying the peritoneum itself are meagre in size and number. The **lymphatics** include a superficial network beneath the mesothelium and a deeper plexus of lymph-channels within the stroma. The **nerves** include both myelinated and unmyelinated fibres, the latter being destined for the walls of the blood-vessels. The sensory fibres supplying the parietal peritoneum in many cases are connected with lamellated corpuscles and end-bulbs (Fig. 121).

THE LIVER

The liver, the largest gland in the body, consists of very delicate glandular tissue disposed around the ramifications of the portal vein. Developed

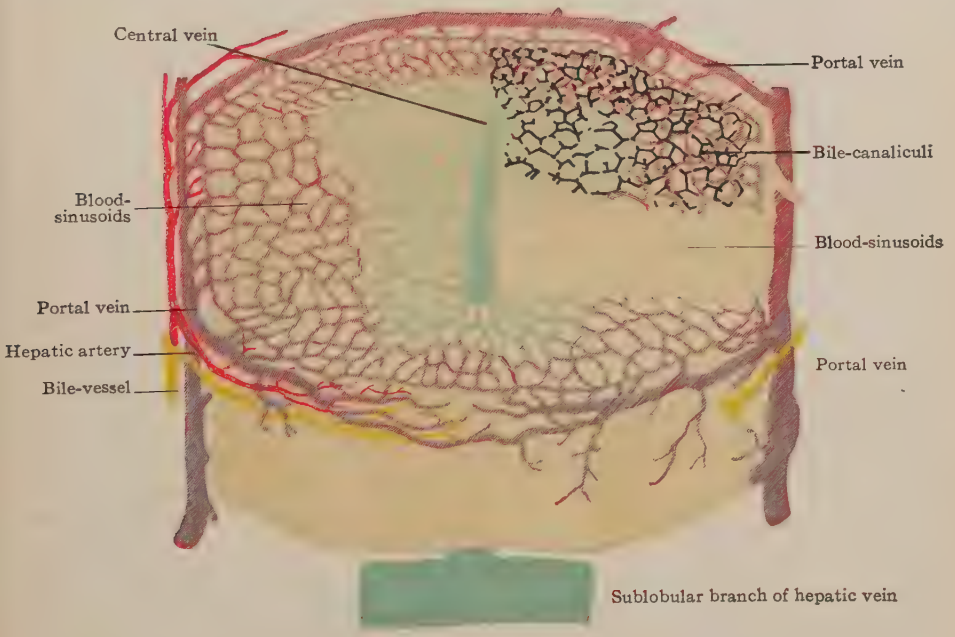


FIG. 220—Diagram of hepatic lobule; portions of surface and of transverse and longitudinal sections of the lobule are represented. The branches of the portal vein are purple; of the hepatic artery, red; of the hepatic veins, blue; of bile-ducts, yellow; the intralobular bile-canaliculi are black.

in the primitive anterior mesentery, its connective tissue (mesodermic) elements have a common origin with the diaphragm, while its duct and glandular elements are derived from a sprout from the entodermal lining of the

duodenum. Hence the liver is an outgrowth and appendage of the alimentary tube. Its peculiar shape is due chiefly to the pressure of surrounding organs since its tissue is so plastic as to be moulded by them. The liver weighs from 1450–1750 gm., approximately 3–3¾ lbs., and in the adult contributes about one fortieth of the entire body weight.

In its fundamental arrangement the liver corresponds to a highly modified compound tubular gland. Early in fetal life, however, the terminal divisions of the tubules unite to form networks, after which the tubular character of the liver becomes progressively more masked by the intergrowth of the cell-cords and the large veins. The glandular tissue is subdivided by connective tissue into small cylindrical masses, the **lobules,** which on the surface of the organ are seen as little polygons, 1-2 mm. in diameter. In pig's liver

FIG. 221—Section of liver injected from hepatic vein, showing intralobular capillary network. × 100.

the average weight of a lobule is 2.41 milligrams, and the average number of lobules in the entire liver is 702,000 (F. P. Johnson, '18). The interlobular tissue is continuous with the fibrous envelope, or **capsule**, that invests the exterior of the liver, at the transverse fissure, or **porta,** being prolonged as the **fibrous capsule of Glisson** into the organ in company with the interlobular vessels. The distinctness with which the lobules are defined depends upon the amount of the interlobular tissue. This is notably abundant in the hog's liver, in which the lobules appear as sharply marked polygonal areas. In the human liver, on the contrary, the interlobular tissue is very meagre, the lobules, in consequence, being poorly defined and uncertain in outline (Fig. 222).

The Blood-Vessels of the Lobule.—The arrangement of the blood-vessels is the salient feature in the architecture of the fully formed hepatic lobule. The divisions of the portal vein and the hepatic artery enter at the porta and break up into branches which ramify within the interlobular tissue (capsule of Glisson) and encircle the lobules. These **interlobular veins** and

arteries give off numerous small branches that enter the periphery of the lobules to resolve at once into the **intralobular sinusoidal network.** The general disposition of this network is radial, the sinusoids converging towards the middle of the lobule where they join to form and empty into the **central,** or **intralobular, vein.** The course of the latter corresponds with the

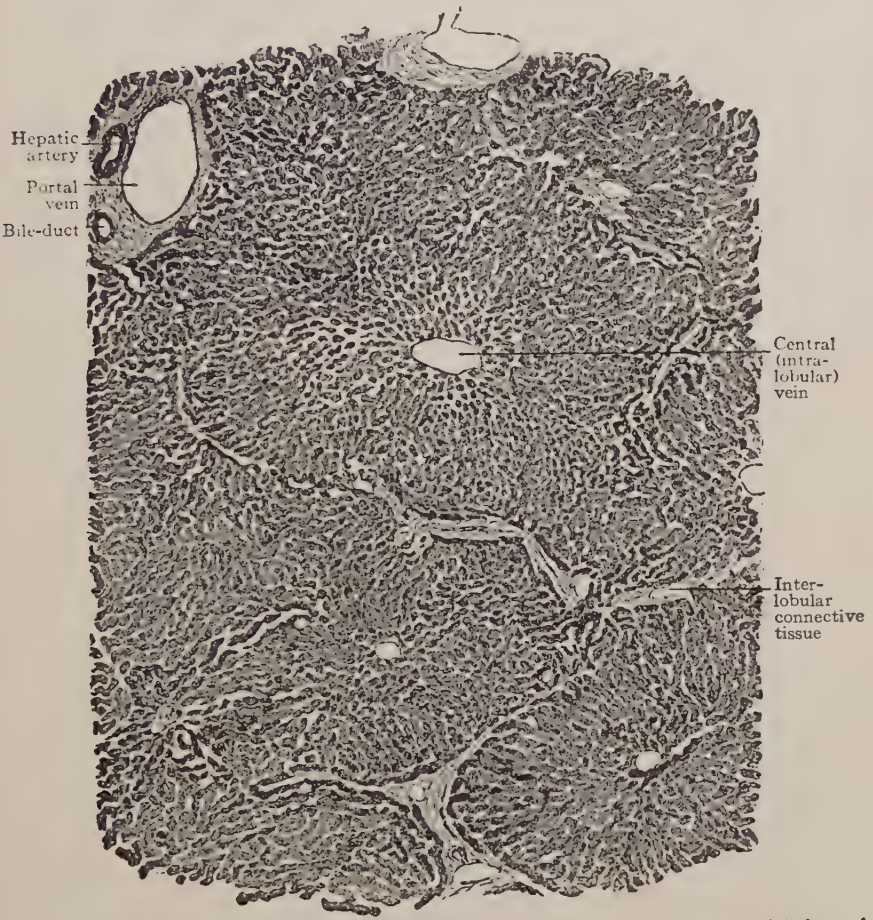


FIG. 222—Section of uninjected liver, showing the general arrangement of the lobules, interlobular and intralobular vessels. × 120.

long axis of the lobule, hence, in cross-sections of the lobule, the central vein appears as a transversely cut channel towards which the sinusoids converge (Fig. 221). The **sinusoidal network** within the lobule is made up of vessels usually about 10 μ in diameter, the widest sinusoids (20 μ) being in the immediate vicinity of the afferent and efferent veins. The meshes of the sinusoidal network vary from 15–45 μ in their greatest dimension, those at the periphery being broader and more rounded, while those near the centre of the lobule are narrower and more elongated.

The central vein traverses the axis of the lobule, enlarging as it proceeds to the **base,** as the side of the lobule through which the vein escapes is termed. The central vein begins usually about midway between the base and the opposite border of the lobule and is formed by the confluence of the sinusoids. Immediately on emerging from the lobule, the central vessel opens into **a sublobular vein,** which runs, in a general way, at right angles to its intralobular tributaries and along and beneath the base of the lobules. The sublobular veins are thus surrounded by the bases of the lobules, a single central vein returning the blood from each. The sublobular veins join to form larger trunks, which in turn unite and constitute the branches of the **hepatic veins,** the large venous channels, commonly several, that carry the blood from the liver into the inferior vena cava.

The Liver-Cells.—The meshes of the intralobular sinusoidal network are occupied by the hepatic cells, the bile-canaliculi and a meagre amount of delicate connective tissue. The liver-cells are arranged as cords, or trabeculæ, which conform in their general disposition and shape to the intervascular spaces which they fill. When isolated, the liver-cells present a polygonal outline and measure from 15–25 μ in their longest dimension. Each cell comes into contact with from six to nine other ones, the surfaces of contact being plane from mutual pressure. Always one side, often more than one, exhibits a shallow concavity that indicates the surface of former contact with a sinusoid. The cells lie against at least one sinusoid and sometimes several, this relation depending upon the size of the blood-channel. The liver-cell consists of finely granular protoplasm, which at times exhibits a differentiation into an outer and inner zone. It is without a cell-membrane, although the cytoplasm is condensed at the periphery. The spherical nucleus contains relatively little chromatin and usually a nucleolus. Occasional cells are conspicuous on account of their large size and unusually large nucleus; such nuclei probably undergo division and produce the double nucleated cells constantly encountered in sections of normal liver. Centrosomes have also been observed. Particles of glycogen, minute oil drops, and granules of bile-pigment are fairly constant inclusions. Fat-containing cells are most abundant at the periphery of the lobule, those containing pigment particles near the centre.

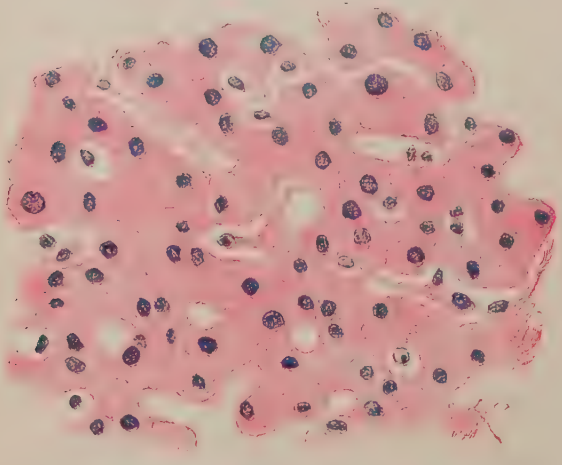


FIG. 223—Section of uninjected liver, showing cords of hepatic cells between the sinusoids. × 400.

The Bile-Canaliculi.—These minute canals, representing the lumina of ordinary tubular glands, form a network of intercommunicating channels throughout the lobule, closely related to the liver-cells. Instead of the arrangement usual in glands, where several secreting cells border the gland-lumen each with a single surface, in the exceptional case of the liver the excretory channels are bounded by the opposed surfaces of only two cells, the bile-canaliculus occupying but a small part of these surfaces, which it models with a narrow groove. Moreover, the canaliculi are not limited to a single surface on each cell, for they are found between all surfaces where two liver-cells are directly in contact. Hence, each hepatic cell is in immediate relation with a number of bile-canaliculi. The latter, however, never

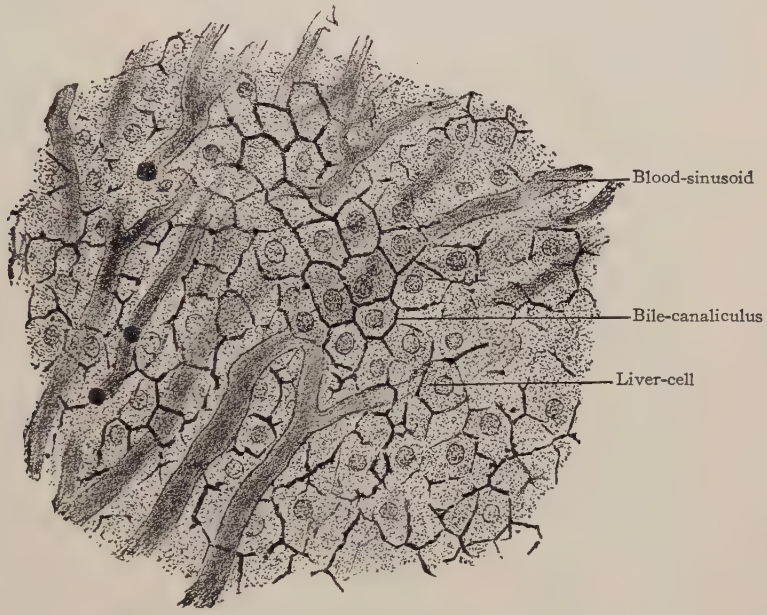


FIG. 224—Section of liver in which both the blood- and bile-canaliculi have been injected; the biliary channels surround the individual liver cells. × 300.

lie on the surfaces of the liver-cells directed towards the blood-channel, the bile-canaliculus never separating the blood-capillary and the liver-cell. Whilst the dominating direction of the bile-capillaries is radial and corresponds to the general disposition of the trabeculæ of hepatic cells, this radial arrangement is converted into a network by numerous cross-branches (Fig. 225). The resulting meshes agree in size and form with the individual liver-cells, which often appear surrounded by the bile-canaliculi. The latter possess no walls other than the substance of the liver-cells between which they lie. The diameter of the minute biliary canals (1–2 μ) remains constant throughout the lobule until the canaliculi reach the margin. Here the liver-cells abruptly diminish in size and become continuous with the low cuboidal cells that line the excretory tubes passing from the lobule into the surrounding connective tissue to become tributary to the larger interlobular

bile-ducts. The ultimate relations between the bile-canaliculi and the liver-cells is still a subject of discussion. According to some, extensions of the canaliculi normally exist within the substance of the cells, thus forming **intracellular secretion-canaliculi.** The latter are sometimes pictured as ending in minute dilatations, the **secretion-vacuoles.** It is highly probable that such appearances, while not artefacts, at least depend upon particular conditions of secretory activity and are, therefore, not constant details of the hepatic cells.

The **intralobular connective tissue** is very meagre in amount and consists of delicate prolongations of the interlobular fibrous tissue along the sinusoids. The tissue occurs only between the blood-channels and cells, and never between the cells. Although present in some quantity immedi-

FIG. 225—Section of liver treated with Golgi method, showing part of intralobular network of bile-canaliculi. × 200.

FIG. 226—Artificially digested section of liver, showing supporting interlobular fibrous tissue (below) and intralobular reticulum (above). × 200.

ately around the central vein, in other parts of the lobule it is represented by lattice-works of delicate fibrils, the entire intralobular connective tissue belonging to the variety known as reticular. The small spindle, or stellate, elements seen in the walls of the sinusoids are known as the **cells of Kupffer,** and represent endothelial cells of a specialized form which is highly phagocytic. For this reason they are regarded physiologically as belonging to the reticulo-endothelial system of the body.

The Biliary Passages.—The **interlobular bile-ducts,** which receive the canals that pierce the periphery of the lobule as outlets of the intralobular network, accompany the branches of the portal vein and of the hepatic artery within the connective tissue between the lobules. The ducts, from 30–50 μ in diameter, form a network over the exterior of the lobule and possess walls consisting of a delicate fibro-elastic coat, in the smallest tubes little more than a basement membrane, lined with low columnar epithelium continuous with the cuboidal cells clothing the emergent canals. The perilobular ducts are

tributaries of larger bile-vessels, which increase in diameter as they pass towards the porta.

The large ducts join into two main lobar trunks, by whose union, within or just beyond the porta, the **hepatic duct** is formed, a tube from 4–6 mm. in diameter and about 2.5 cm. long. Its walls include a dense fibro-elastic tunica propria, covered with a single layer of columnar epithelium and beset with scattered small tubular **glands.** These, as well as the surface epithelium, contain many goblet-cells producing a mucous secretion. Bundles of unstriped muscle occur within the deeper parts of the tunica propria; they are neither numerous nor regularly disposed in definite layers, the chief longitudinal one being supplemented by circular and oblique bundles. As the duct system is followed into the capsule of Glisson, the muscle disappears from the walls of all but the larger interlobular bile-

FIG. 227—Section of liver, showing interlobular tissue and vessels. × 160.

vessels, while the fibro-elastic coat also gradually diminishes. Apart from the reduction in height of the cells, the lining of the ducts retains throughout its character of simple columnar epithelium, thus affording a ready means of distinguishing the bile-ducts from the blood-vessels as they course together between the lobules.

The **gall-bladder,** the pear-shaped receptacle for the bile attached to the under side of the liver near its anterior border, possesses walls consisting of three coats: the **mucous,** the **muscular,** and the **fibrous,** the latter supplemented by a more or less extensive investment of peritoneum. The **mucous coat,** covered with a single layer of columnar epithelium 20–25 μ thick, is modelled by a network of slightly raised ridges that mark off irregular polygonal areas some 5 mm. in diameter. These areas are often marked by minute tubular depressions of the mucosa which have been mistaken for glands. True branched mucous glands occur only in the neck of the gall-bladder.

The epithelial cells exhibit a cuticular border and have absorptive functions, inasmuch as they absorb water and perhaps other substances from the bile. This brings about the **inspissation** of the bile in the gall-bladder, and makes it different in appearance and consistency from that in the hepatic ducts, coming directly from the liver. The tunica propria contains a profusion of elastic fibres intermingled with the white fibrous tissue. The **muscular coat** is composed for the most part of circular bundles of unstriped fibres, but with these are interwoven longitudinal and oblique ones. Outside the muscle lies a dense fibrous coat of fibro-elastic connective tissue. Where invested with peritoneum, the latter is attached to the proper wall of the sac by a layer of fat-laded subserous tissue.

The **cystic** and **common bile-ducts** possess walls that in structure cor-

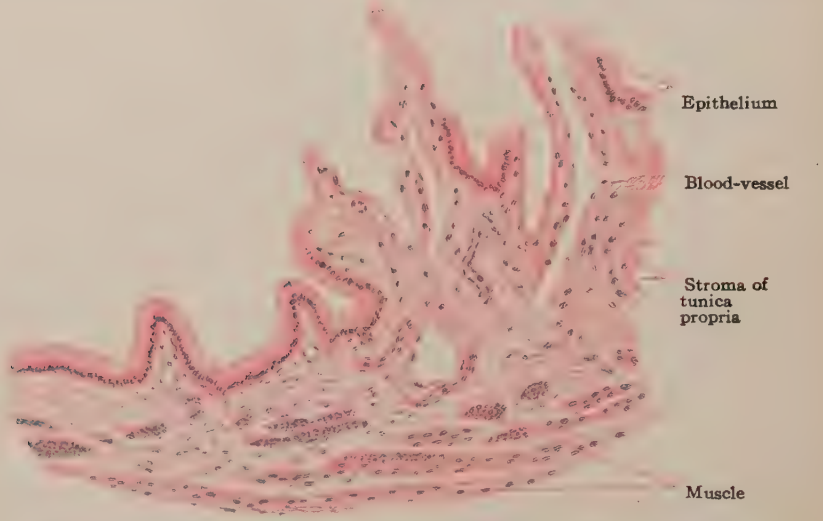


FIG. 228—Section of wall of gall-bladder, showing plicated condition of mucous membrane. × 100.

respond with the hepatic duct above described, consisting of a mucous tunic strengthened by bundles of unstriped muscle. Within the mucous membrane are many glands and diverticula. These diverticula may in part take over the function of the gall-bladder when the latter is removed surgically (Sweet). At the lower end of the common bile-duct, the circular fibres are greatly augmented and form a sphincter-like ring around the orifice of the tube where it opens through the intestinal wall at the duodenal papilla of Vater. The **bile,** the secretion of the liver, contains no distinctive cells; numerous oil drops, and granular masses of biliary pigment, with occasional remains of the epithelial cells lining the ducts, being the more common objects encountered when the fresh fluid is examined microscopically.

The **blood-vessels** of the liver—the portal vein, the hepatic artery, and the emergent hepatic veins—have been already described. It should be noted, however, that the blood conveyed to the organ by the hepatic artery is destined for the oxygen-supply of the interlobular structures, the

capsule of Glisson, and the walls of the blood-vessels and of the bile-ducts. After supplying these through numerous although small twigs, the blood is collected by venous radicles and emptied either into interlobular branches of the portal vein or into the intralobular sinusoidal network.

The **lymphatics** of the liver are represented within the lobules by minute tissue-spaces between the blood-channels and the liver-cells. These spaces drain into the more definite lymphatic paths within the interlobular connective tissue, which as the **deep lymphatics** surround the blood-vessels and ducts with plexuses that condense into the fifteen or more trunks emerging at the transverse fissure. The **superficial lymphatics,** very numerous and freely communicating with the deep set, arise from a close-meshed network of lymph-channels within the fibrous capsule.

The **nerves** of the liver, from the cœliac through the hepatic plexus, consist mostly of unmyelinated fibres, very sparingly intermingled with myelinated ones. The former are destined chiefly for the walls of the blood-vessels and of the larger ducts, which, after sending filaments to the capsule, they follow within the interlobular tissue, where occasional nerve-cells are found along their course. Some fibres, probably secretory in function, penetrate the lobules to end between the liver-cells. The few myelinated fibres terminate within the interlobular tissue.

THE PANCREAS

The pancreas is a large tubo-alveolar gland that lies behind the stomach extending from the loop of the duodenum across the spine and left kidney,

FIG. 229—Section of pancreas, showing general arrangement of lobules. × 30.

often as far as the spleen. It is conventionally divided into the head embraced by the duodenum, the body, and the tail. The interlobular connective tissue is unusually abundant; hence the compartments of gland-tissue are

loosely united and the entire organ lacks the compactness ordinarily seen in large glands. While agreeing in its general structure with serous salivary glands, as the parotid, the pancreas differs in certain particulars. The most important of these are: (**a**) long intermediate ductules instead of intralobular ducts, for the conveyance of the secretion to the ducts between the lobules; (**b**) the presence of the characteristic islands of Langerhans; (**c**) the marked differentiation of two zones in the cytoplasm of the secreting cells.

The chief **pancreatic duct,** whose walls consist of a single layer of distinct tall (12–14μ) columnar epithelium and a tunica propria of compact fibro-elastic tissue, gives off numerous lateral interlobular branches, also lined by a simple although lower epithelium. The canals springing from

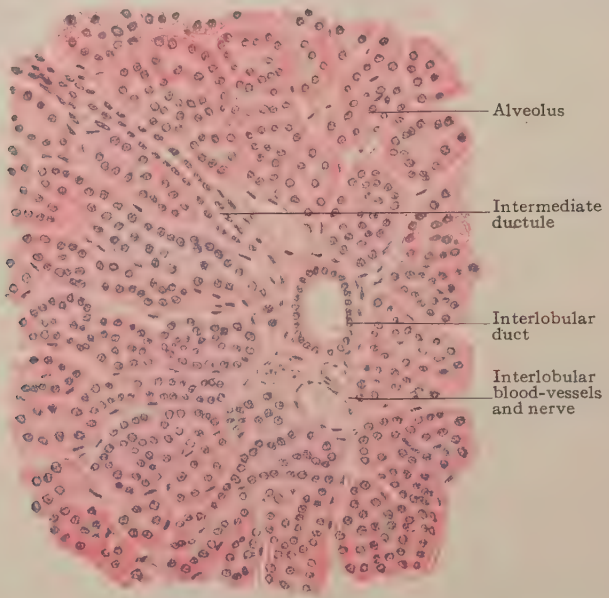


FIG. 230—Section of pancreas, showing interlobular tissue with vessels, nerve, and duct and surrounding tubular alveoli. × 200.

the interlobular ducts enter the lobules, where they are lined by flattened epithelial cells (3 μ high) and correspond to intermediate ductules and not to the usual intralobular ducts. The latter being wanting, the uncommonly long intermediate ductules pass directly from the tubular alveoli to the interlobular ducts. Where the thin ductule-epithelium joins that of an alveolus, there is a slight telescoping of the former within the latter. These flat cells seen within the alveolus are called **centroalveolar cells,** and where present, they partly exclude the alveolar cells from direct relation with the lumen. Intercellular **secretion-canaliculi** are present in all alveoli in which the centroalveolar cells exclude the gland-cells from the lumen. They extend between the cells, almost but not quite, to the basement membrane (Fig. 231) and serve to convey the secretion-products between the obstructing central cells into the lumen of the alveolus. The relation of the centroalveolar

cells to the secretory elements within the alveolus is such that the thinned-out duct-cells are invaginated into the alveolus, so that the glandular epithelium is partly excluded from direct relation with the lumen.

The tubular **alveoli,** often tortuous and sometimes divided, possess a well-defined basement membrane, against which lie the gland-cells. The latter are usually blunt pyramidal in shape, with a length of about 12 μ. Their cytoplasm exhibits two well-differentiated zones, an inner granular one, next the lumen, filled with highly refracting zymogen granules, and an outer clear one, next the basement membrane, which is free from granules and contains the spherical nucleus. The relative width of these zones varies with the functional condition of the cells. During rest, when the cells are stored with zymogen particles, the granular zone is very broad and the outer homogeneous one correspondingly narrow. With discharge of the pancreatic secretion during digestion, the granular zone diminishes and reaches its minimum, almost disappearing when the gland is exhausted. The return to a condition of rest is accompanied by the formation and accumulation of a new store of zymogen particles until the granular zone is again at its maximum.

FIG. 231—Portion of pancreas, treated with Golgi method, showing secretion-canaliculi extending between the gland-cells. × 50.

The **interalveolar cell-groups,** or **islets of Langerhans,** appear as small masses of modified gland-tissue, some 3 mm. in diameter, lying between the tubular alveoli, from which they are separated by delicate envelopes of fibrous tissue. The total number in the human pancreas has been found to vary from 200,000 to 1,760,000 (E. Clark, '13). They are always more numerous in the splenic end of the pancreas than in its other parts. These bodies consist of anastomosing solid cords, or trabeculæ, of small polyhedral cells, faintly granular and without zone differentiation, separated by wide capillary blood-vessels, with which the interalveolar cells come into intimate relation, the vascular endothelium alone intervening. There are two types of glandular cells which are distinguishable only by precise cytological methods; these have been called the α and β islet-cells. The cell-groups appear isolated from the alveolar tissue, but connections have been seen in man and in other species, and the relation between the islet-cells and the ordinary glandular parenchyma is still uncertain. Developmentally, the

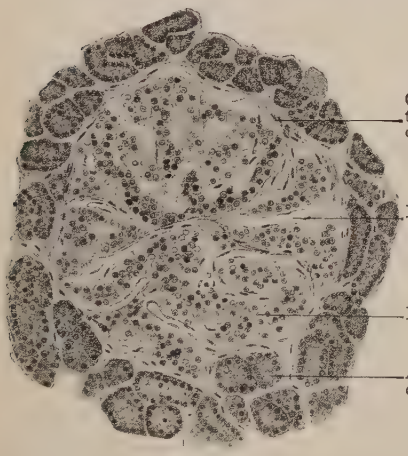


FIG. 232—Section of pancreas, showing details of island of Langerhans. × 190.

islet-cells and the ordinary glandular elements are derived from a common source, but differentiation having once been established, probably there is no interchangeability between the two varieties of epithelium. Independence of function is generally conceded, and, the islets are to be regarded collectively as an organ of internal secretion, producing a substance, **insulin**, which enters the blood and serves an important purpose in regulating carbohydrate metabolism.

The **pancreatic duct,** or **duct of Wirsung,** empties into the second part

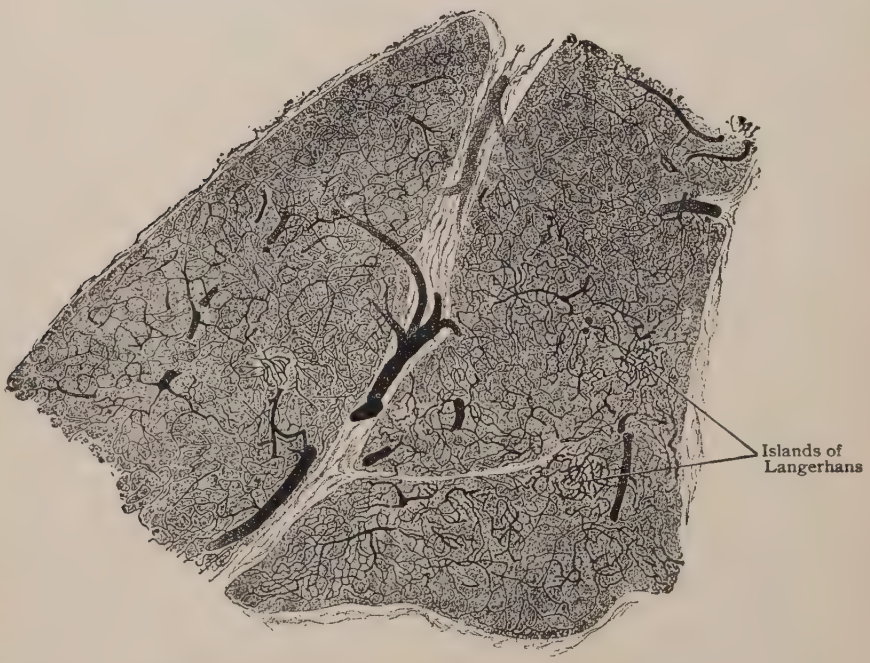


FIG. 233—Section of injected pancreas, showing intralobular capillary network; also vascular convolutions of islands of Langerhans. × 50.

of the duodenum through the duodenal papilla alongside the common bile-duct. Typically the two ducts are separate to the tip of the duodenal papilla. Frequently there is an enlargement of the end of the pancreatic duct, forming a sinus-like dilatation which almost encloses the bile-duct. The walls of the main duct and its larger branches contain numerous small tubular mucous glands and bundles of unstriped muscle both circular and longitudinal. At its lower end, the circular bundles are condensed and augmented into a sphincter-like band that encircles its duodenal orifice. The duodenal mucosa at the papilla is extremely redundant, with many pointed processes directed toward the tip of the papilla.

The **blood-vessels** supplying the pancreas are distributed to the glandu-

lar tissue in accordance with the usual plan for such structures. The positions of the groups of islet-tissue, however, are indicated in minutely injected organs by close-meshed areas in which the capillary network is exceptionally dense (Fig. 233). The **lymphatics** are represented by definite channels accompanying the interlobular blood-vessels to which the intralobular tissue-spaces are tributary. The **nerves** are composed chiefly of unmyelinated sympathetic fibres distributed to the walls of the blood-vessels and of the larger ducts, some passing to the alveoli. Ganglion-cells, scattered or grouped, lie along the interlobular trunks.

ENDOCRINE GLANDS

The endocrine glands are also called ductless glands because although they form secretions, these are not carried away by duct-systems, but pass into adjacent fluids as blood, lymph, or cerebro-spinal fluid. When the secretions mingle with these fluids they are distributed by them to all parts of the body and thus have a widespread influence on the tissue and organs. These secretions are known as internal secretions, as distinguished from those of the exocrine glands, as the salivary, liver, and mammary glands, where the secretion-products are collected by a series of tubes and conveyed by larger ducts to definite localities. Internal secretions are synthetic products of the cell-activities, and ordinarily do not include katabolic products. Histologically, the secreting cells are regarded as glandular epithelium, and these are arranged in networks or columns, and are supported by fibrous connective tissue in which run many blood-vessels which come into intimate relation with the glandular cells.

THE THYROID GLAND

The thyroid gland is developed from an unpaired median rudiment. This median rudiment, or anlage, is an entodermic epithelial outgrowth from the anterior wall of the primitive pharynx in the region of the second visceral arch and in close relation with the posterior part of the tongue. The position of this outgrowth is later indicated by a depression on the tongue, the foramen cæcum, just behind the apex of the row of circumvallate papillæ. The anlage grows ventrally and subsequently forms the definite thyroid surrounding the respiratory tube. The histogenesis of the organ includes: (**a**) numerous cylindrical epithelial cords from which grow out lateral branches; (**b**) fusion of these cords into a network whose meshes are filled with vascular mesodermic tissue; (**c**) severance of the epithelial reticulum into masses corresponding to the later follicles; (**d**) the appearance, within these masses, of lumina around which the cells become arranged as the epithelial lining of the compartments subsequently containing the characteristic colloid substance. The thyroid body agrees with the parathyroid and the thymus in arising from the walls of the primitive pharynx and in deviating during its later development from its original likeness to a typical gland.

The thyroid gland is situated in the neck, in front and at the sides of the upper end of the trachea, and consists of two **lateral lobes** connected by a narrow strip, the **isthmus.** Although during its early development corresponding in principle with compound alveolar glands, the fully formed thyroid gland possesses no excretory ducts and varies in the details of its terminal compartments. The fibro-elastic **capsule** investing the organ gives off septa which subdivide the lobes into a number of tracts, each composed of smaller masses, the **primary lobules,** separated by thin partitions of con-

nective tissue. These subdivisions (.5–1 mm. in diameter) contain a variable, but usually large, number of **follicles,** which correspond to the alveoli of ordinary glands and are supported by a highly vascular fibro-elastic framework.

The **follicles,** ellipsoidal or cylindrical sacs, vary greatly in size (50–200 μ), depending upon the amount of the contained secretion and distention. They are lined by a single layer of fairly regular epithelial cells, usually cuboidal, although they may approach either the columnar or the flattened type. Their spherical nuclei are surrounded by clear cytoplasm, which often contains granules of a fatty nature. The epithelial cells are the source of the peculiar soft acidophil substance, **colloid,** the material that fills and distends to a variable degree the follicles. Some of the latter may appear very small and tubular and contain no secretion, while the neighboring follicles are enormously distended with masses of colloid. As usually seen in

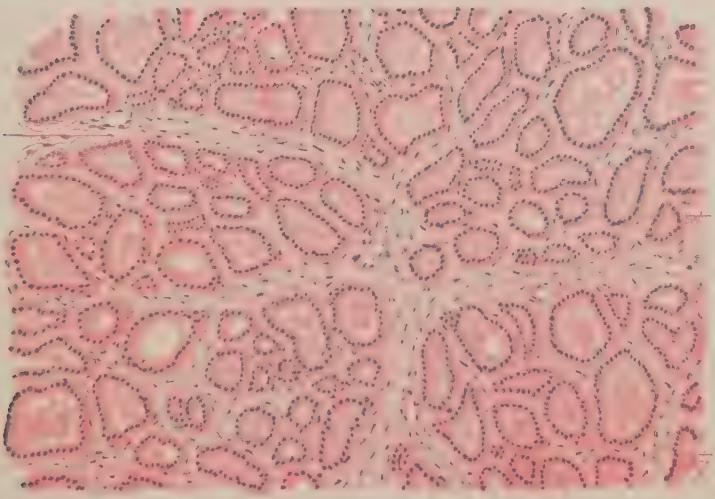


FIG. 234—Section of thyroid body, showing follicles in various degrees of distention. × 100.

sections, the colloid substance is homogeneous or finely granular and often partly detached from the lining cells by shrinkage. Vacuoles are also common and contain materials of a mucous or fatty nature. Large granular elements, **interstitial cells,** occur within the connective tissue between the follicles.

Cytological Changes Accompanying Formation of Colloid.—These have been studied by Ma ('25) in the thyroid of the albino rat, and he finds the following stages:—(**a**) Exhausted cells, (**b**) Regeneration, (**c**) Final presecretion stages, ripening of the presecretion; (**d**) Formation and extrusion of secretion, secretory discharge. The exhausted cells are most frequently of cuboidal epithelial type. Some, however, are columnar, and others lower than cubical. The cytoplasm takes little stain and is very watery in appearance. The nucleus is irregular in form and shrunken.

The first striking progressive change in the regenerating cell is the appearance and spread of a homogeneous basophilic substance in the

cytoplasm. The basophilic substance is a new chemical product within the cells and first appears close to the basement membrane, in the end of the cell into which the raw material enters from the blood-stream. From this end it gradually spreads throughout the cytoplasm towards the follicular lumen. In this homogeneous basophilic substance mitochondria appear. At first they are granular, then rod-shaped forms, and finally filaments are seen. All these forms are intermingled. The longer forms often lie lengthwise in the cell, curving around the nucleus. As the mitochondria become numerous the basophilic substance becomes less evident and is apparently being utilized in the formation of mitochondria. The nuclei are round or ovoid. At first they are near the base of the cell and are palely-staining, but towards

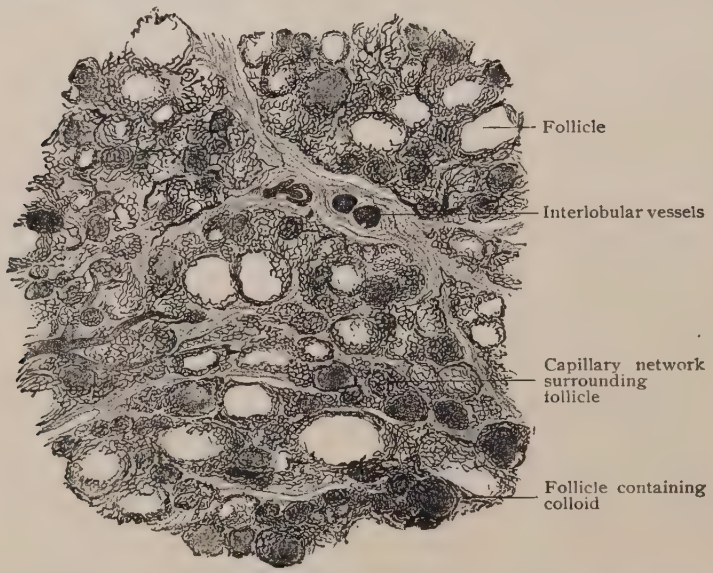


FIG. 235—Section of injected body, showing rich capillary networks surrounding follicles. × 46.

the end of this period they are centrally placed, their chromatin substance has increased, and they have a well-defined nuclear membrane.

When there is a considerable amount of colloid already present in the lumen of the follicle the next stage is as follows. Little vacuoles appear in the cytoplasm near the lumen. Often the inner end of the cell is almost entirely comprised of these vacuoles. The mitochondria adjacent to the vacuoles usually break up into granules, and at the same time become swollen. They then gradually disappear in the substance of the vacuoles and, from this union the colloid material is formed. It is probable that the vacuoles while yet in the cell fuse and form larger ones, since a great range of sizes is found. The vacuoles with the dissolving mitochondria then leave the cell and pass into the periphery of the lumen as pale droplets. The colloid according to this interpretation is the result of the interaction of the contents of the fluid vacuoles and the mitochondria.

The **blood-vessels** supplying the thyroid tissue are unusually plentiful, the interlobular arteries, branches from the superior and inferior thyroids, breaking up into close networks that surround the follicles and lie immediately beneath the epithelium. The **lymphatics** also abundant, begin as perifollicular tissue-spaces, from which are formed the interlobular lymphatics accompanying the blood-vessels. The deeper lymphatics join the superficial plexus, on the surface of the organ, from which the larger trunks pass in different directions. The **nerves** are, for the most part, sympathetic fibres supplying the walls of the blood-vessels and enclosing the follicles in plexuses of unmyelinated filaments, which end in close relation with the epithelial cells.

THE PARATHYROID GLANDS

These little glands, also called the **epithelial bodies,** when typically present are arranged as two pairs, an upper and a lower. The upper ones are the more constant and usually lie against the posterior surface of the lateral thyroid lobes. The inferior bodies are less constant, both as to posi-

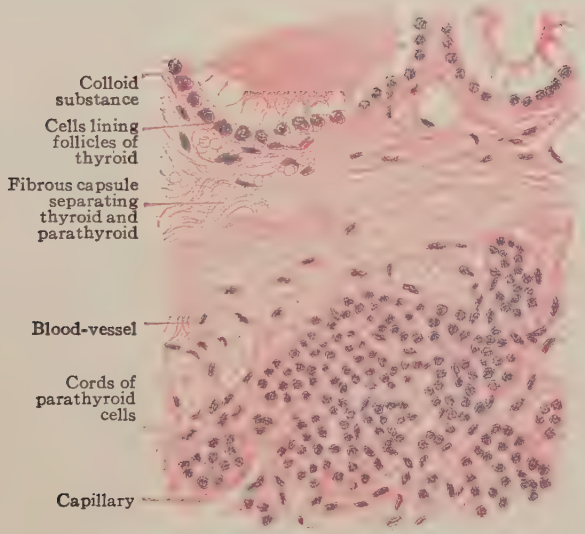


FIG. 236—Section including adjacent portions of human thyroid (above) and parathyroid (below). × 220.

tion and presence, sometimes lying against the side of the trachea under cover of the lower part of the thyroid lobes, or upon the latter, and at other times being placed entirely below the thyroid. The disposition of the parathyroids may be asymmetrical, in some cases as many as four, in others none, lying on one side. The bodies are 6–7 mm. long, 3–4 mm. broad, and 1.5–2 mm. thick, but may be larger or smaller. They arise from the dorsal wall of the third and fourth pharyngeal furrows and thus differ from the thyroid body in origin, as well as structure.

Each organ is invested by a thin fibro-elastic **capsule** and subdivided

into **lobules** by delicate septa, which support the larger blood-vessels. The distinctive tissue consists of closely-placed polygonal **epithelial cells** disposed as continuous masses or as imperfectly separated cords and alveoli. The cells have round nuclei and are lodged within a reticulum composed of wide capillaries and delicate strands of fibro-elastic tissue, the whole often bearing a striking likeness to the anterior lobe of the pituitary body even to the presence of colloid substance within some of the alveoli. The great majority of the cells, the **chief** cells, are small, with palely-staining cytosomes and deeply-staining nuclei. The pale coloration of the cytosomes is due to the presence of minute spherical globules of fat. At adolescence, a second type of cell appears. This is a large polygonal cell, with its cytosome filled with acidophilic granules, and having a relatively pale nucleus. They are known as **acidophiles** or *oxyphil cells*, and increase in number as age advances. When the cell-masses tend towards the alveolar type, the epithelium and the blood-channels are in intimate relation, an arrangement probably facilitating the distribution of the particular product of the cells. The significance of the parathyroid bodies as distinct organs with a special function in calcium metabolism has been established; in certain animals, their loss results in tetany and death.

The **blood-vessels** supplying the organs are the minute parathyroid arteries, usually from the branches of the inferior thyroid, to each one of which a body is attached. The capillaries are relatively wide and ramify between the nests of cells. Little is known concerning the **lymphatics** and **nerves**; the latter, however, are chiefly sympathetic fibres for the walls of the blood-vessels.

THE ADRENAL GLANDS

The **adrenals,** or **suprarenals,** are a pair of glands about 6.5 cm. long and half as broad, situated at the back of the abdominal cavity, on the inner aspect of the upper ends of the kidney.

The adrenal gland is invested by a distinct fibrous **capsule,** from which delicate septa pass into the organ, forming a framework of connective tissue for the support of the blood-vessels and the cellular constituents. Section across the thicker parts of the body displays an outer zone, the **cortex,** from .25–1.25 mm. in thickness, which encloses a central area, the **medulla.** Towards the borders of the organ, the medulla is reduced to a narrow zone, or may be entirely wanting; where best developed, as in the middle, it may attain a thickness of over 3 mm. The cortex is usually of a dull yellow color, next the medulla presenting a narrow band of varying shades of brown. The medulla is of a grayish tint and generally lighter than the cortex. Its exact color, however, varies with the amount and condition of the contained blood, when engorged with venous blood being dark. Embryology and comparative anatomy indicate that the mammalian adrenal gland includes two entirely distinct organs, which, although intimately united as the cortex and medulla, possess different origins and functions. The cortex arises from mesenchyme within the dorsal wall of the body-cavity, immediately cephalad of the metanephros. The medulla is formed by the migration of

embryonic sympathetic neurones, the medullary cells closely corresponding with the chromaffin elements elsewhere originating from the sympathetic.

The **cortical substance** consists of a delicate framework of connective tissue, prolonged from the capsule, in whose meshes lie the tracts of the distinctive epithelial cells. The cortex is not always uniform, but often subdivided into indistinct subcapsular lobules by thicker septa continued from the overlying fibrous investment. The arrangement of the cortical cells, although in a general way columnar or slightly radial in the peripheral lobular areas, varies at different levels, three zones being distinguished within the cortex (Fig. 238). The narrow **zona glomerulosa** lies next the capsule and consists of more or less rounded cell-groups. The **zona fasciculata** forms the major part of the cortex and is made up of parallel or slightly radially disposed cell-columns. The **zona reticularis,** next the medulla and narrow, includes the networks of epithelial elements formed by the union of the inner ends of the columns of the preceding zone. The cells throughout the cortical strands are fairly similar, being rounded polygonal elements, 15–20 μ in diameter, whose cytoplasm lodges a variable, but usually large number of fat globules. The latter are very abundant in the cells of the zona fasciculata, but few or entirely absent in those of the zona reticularis. Within the last named region, however, the cells are more or less pigmented, a peculiarity accounting for the darker tint of this part of the cortex (Fig. 238). The cells composing the cords and columns are in direct contact with one another; as groups, they are not surrounded by a basement membrane, but come into close relation with the capillary blood-vessels that enclose the cell-islands, a few delicate strands of supporting tissue alone intervening.

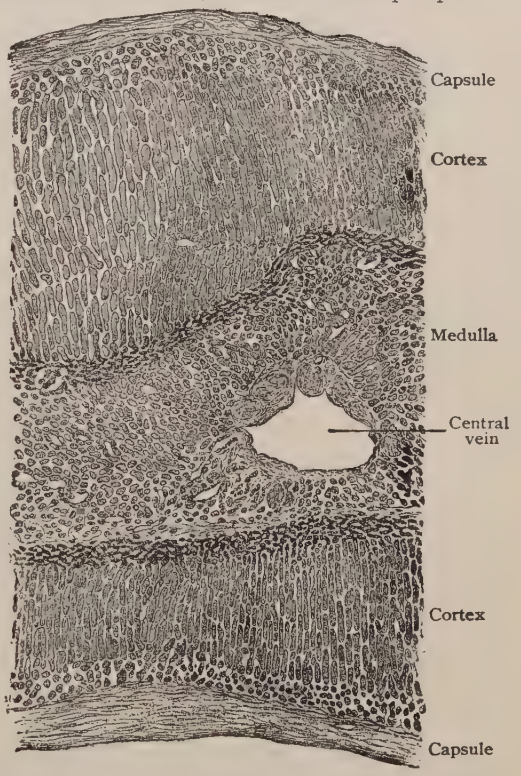


FIG. 237—Section of adrenal gland including entire thickness of the organ, showing the general arrangement of cortex and medulla. × 27.

The **medullary substance** consists chiefly of networks of anastomosing cords of polyhedral cells (20–30 μ in diameter). They are distinguished from the cortical elements by the affinity of their cytoplasm for chromic acid and

its salts, staining yellow or brown. They are known, therefore, as **chromaffin cells,** and regarded as akin to sympathetic elements. These are the cells which form **adrenalin,** the specific secretion of the medullary portion of the adrenal. In addition to these cells, the medulla contains numerous blood-vessels, particularly venous channels, and many bundles of nerve-fibres and ganglion-cells. The latter (Fig. 239) occur singly or in small groups, are multipolar or stellate and resemble the cell-bodies of sympathetic neurones.

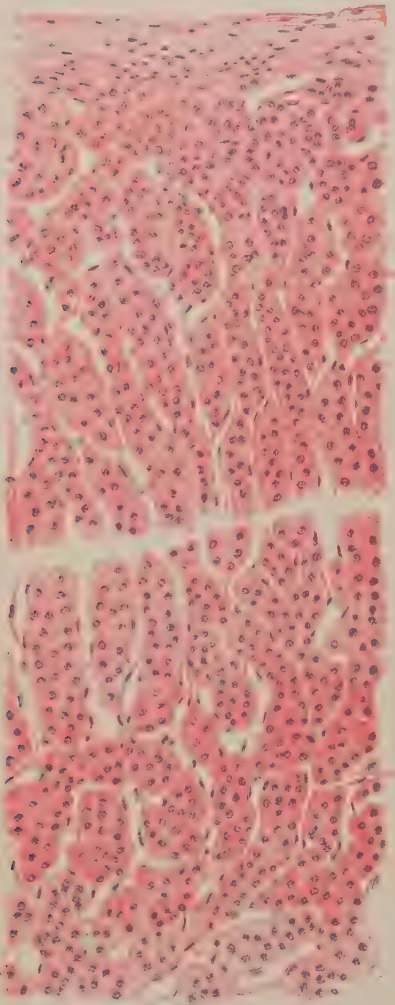


FIG. 238—Section of adrenal gland, showing details of superficial and deep portions of cortex. × 225.

The **blood-vessels** supplying the adrenal gland divide into a dozen or more fine branches which enter by piercing the capsule at various points, some penetrating directly as far as the medulla, but most of them terminating within the cortex. These last form a superficial network from which the capillaries extend between the cell-cords, which are thus enclosed within vascular meshes of corresponding form. Thus, within the cortex the meshes are elongated, and within the medulla rounded, in form. In large part the medulla is supplied by arterioles passing directly to the interior of the organ. These break up into capillaries which surround the medullary cords and, in conjunction with the capillaries of the deeper part of the cortex, pass over into an unusually rich plexus of veins terminating in the large central vessel, the beginning of the chief suprarenal vein. In the walls of the large veins of the medulla there is a peculiar irregular arrangement of longitudinal muscle fibres. On one side of the vein the muscle may be greatly thickened, while on the other side it is of the usual thickness. Superficial veins, arise from the peripheral portions of the cortical capillary network.

The **lymphatics** are represented by a network within the zona

glomerulosa which communicates with the subcapsular plexus, on the one hand, and, by means of centrally directed stems, with the rich medullary plexus on the other. The larger trunks from the medullary network follow the veins and emerge at the hilum of the organ as several efferents that pass to adjacent lumbar lymph-nodes.

The **nerves** are remarkable for their abundance and are derived principally from the solar and renal sympathetic plexuses, fibres from the vagus being included. They form a plexus within the capsule from which bundles of chiefly unmyelinated fibres pierce the capsule, along with the arteries, and give off fibres that pass between the cell-cords of the zona glomerulosa and zona fasciculata to end in the walls of the blood-vessels and on the surface of

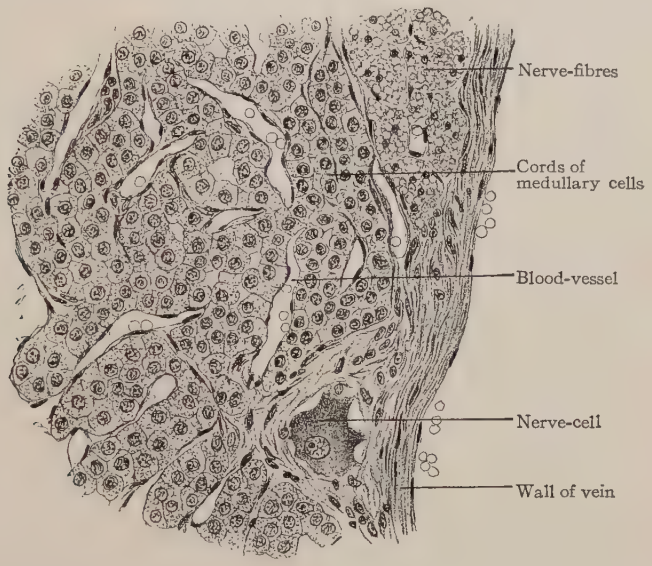


FIG. 239—Portion of medulla of adrenal gland, from vicinity of central vein. × 280.

the cell-groups. Other branches penetrate to the zona reticularis to form a still closer plexus, but it is for the medulla that the most striking abundance is provided. Here the numerous nerves join into plexuses from which fibres pass to the blood-vessels and the cords of medullary cells. In contrast to their superficial relation to the cortical cell-groups, within the medulla the fibrils penetrate between the cells, so that almost each of the latter comes into direct relation with a nerve-fibre. Sympathetic ganglion-cells, isolated or in small groups, are also present, but are not to be found in every microscopic section.

Accessory Adrenals.—These are usually very small, rarely surpassing a pea in size. They may be found near the adrenal body, in the kidney, in the liver, in the solar and renal plexuses, or beside the testis or the ovary. The accessory adrenal situated in the broad ligament of the uterus, in the vicinity of the ovary, is known as **Marchand's organ,** and

regarded as a normal and almost constant organ. These "accessory" bodies include two groups of different origin and morphological significance. Those situated near the chief organ, as when in the liver or kidney, are probably derived from separated and isolated portions of the principal embryonic area of the adrenal and, therefore, are supernumerary. The bodies situated in the broad ligament or in relation with the epididymis, are, on the contrary, probably developed as structures independent of the main adrenal. The independent bodies never, and the supernumerary ones only in very exceptional cases, possess more than cortical substance, a medulla being wanting.

FIG. 240—Section of injected adrenal gland; the vessels in the lower third of figure are chiefly tributary to the central vein. × 25.

Although at present the rôle of the cortical substance of the adrenal is disputed, the special activity of its medulla in producing adrenalin is well established. Adrenalin exerts its influence especially upon the tonus of the involuntary muscle of the blood-vessels and is believed to facilitate the functions of the sympathetic nervous system in various physiological emergencies (Swale Vincent, '25).

THE HYPOPHYSIS CEREBRI

The **hypophysis cerebri,** or **pituitary body,** is attached to the dependent tip of the infundibulum, the narrow funnel-like projection from the floor of the third ventricle. It is of flattened oval form, somewhat mushroom-shaped, and measures about 12 mm. in the transverse and about 7 mm. in the sagittal diameter. Histologically the hypophysis includes two entirely distinct parts, the **epithelial** and **neural** portions, which differ both in origin and structure. The former is derived as an outgrowth from the roof of the primitive oral cavity while the latter is developed as a tubular evagination from the floor of the second brain-vesicle, the diencephalon.

Of the **epithelial portion,** there are three subdivisions—**pars anterior propria, pars intermedia,** and **pars tuberalis.** These are all derived from a hollow outgrowth of epithelium, the **pouch of Rathke,** which arises as an invagination from the roof of the primitive oral cavity. As development proceeds it becomes constricted off, forming a sac with a narrow stalk. Then the sac closes, and the stalk usually disappears. The anterior and posterior walls of the sac differentiate with growth. The anterior wall proliferates actively and for the most part forms a large glandular epithelial mass, the pars

anterior propria. From the epithelium of the anterior wall close to the stalk, lateral processes early appear, and these extend to the under surface of the tuber cinereum, and thus form the pars tuberalis (Atwell, '26). The posterior wall forms a relatively thin plate of cells, constituting the pars intermedia.

The Pars Anterior Propria.—The anterior glandular division, which constitutes the major part of the hypophysis, is surrounded by a robust fibrous capsule that is continuous with the thinner investment enclosing the posterior lobe. From the deeper surface of the capsule, as well as from a condensation of connective tissue on each side of the mid-line that marks the position of large blood-vessels, fine processes extend inward and form a delicate supporting fibrous reticulum, rich in capillaries, whose meshes are filled

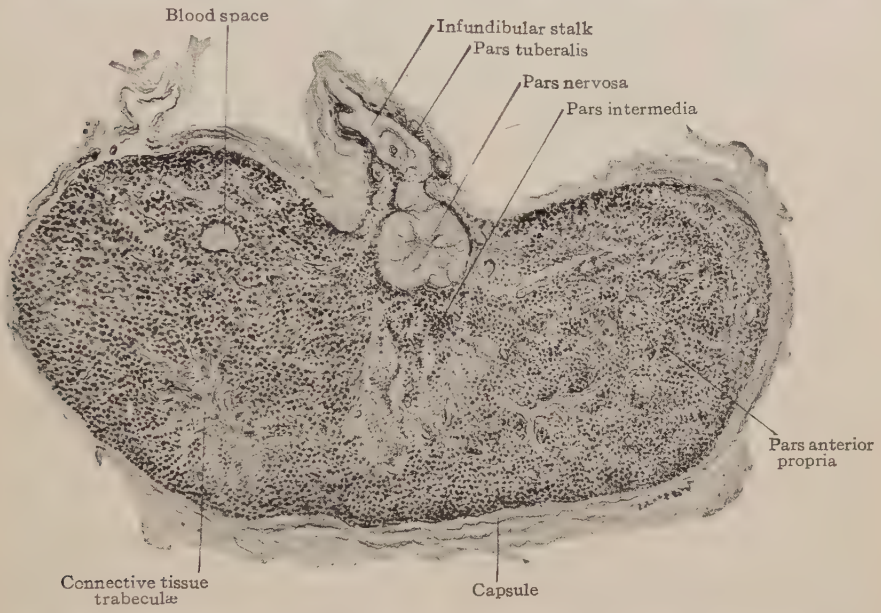


FIG. 241—Horizontal section of hypophysis, showing relation of epithelial and neural portions. × 9.

with spherical or cord-like masses of cuboidal or polygonal epithelial cells. The latter are principally of two kinds—the smaller **chief cells,** or **chromophobe cells,** which are relatively palely-staining cells, and the larger **chromophile cells,** so named because of their affinity for certain dyes. There are two varieties of chromophile cells intermingled in the anterior lobe. The majority stain deeply with acid dyes such as eosin, while the remainder stain with basic dyes.

The aggregations of the cells, cord-like or spherical in form lie in close relation to the capillary blood-vessels that ramify between them, supported by the delicate connective tissue framework. Here and there, however, the glandular epithelium surrounds a lumen which may contain colloid material and thus resemble the alveoli of the thyroid body. Such colloid-containing spaces are specially numerous and large in the zone adjacent to the pars intermedia.

The Pars Intermedia.—The lumen of the pouch of Rathke remains as a cleft between the pars anterior propria and the pars intermedia during childhood, but becomes narrower during adolescence. In the early thirties the cleft usually disappears, and the two adjacent portions of the gland come into contact, finally becoming continuous, and thereafter there is no well-defined line of demarcation (Cooper, '25). There are always vesicles containing colloid, and the bounding cells are frequently flattened. The cells are mainly of two varieties—those containing neutrophile granules and those with basophile granules. Some of the latter tend to invade the adjacent tissues of the pars nervosa in large masses, thus making an irregular boundary-line.

The Pars Tuberalis.—This is a thin epithelial layer which surrounds

FIG. 242—Section of pars intermedia of hypophysis, showing details of structure; three alveoli contain colloid material. × 250.

the infundibulum and spreads out upon the surface of the tuber cinereum. In preparations of the hypophysis, in which the stalk of the infundibulum remains attached to the pars nervosa, portions of the pars tuberalis are seen. The epithelial cells are arranged in small groups surrounded by loose connective tissue.

The Neural Portion, Pars Nervosa.—The posterior division of the pituitary body is directly attached to the floor of the third ventricle by means of its stalk prolonged from the infundibulum. During the early stages of its development, this lobe is represented by a tubular downgrowth whose walls partake of the general character of the parent brain-vesicle. In man the lumen within the lower end of the diverticulum later entirely disappears, the posterior lobe being solid, but in many other mammals, as in the cat, the lumen is retained. In the adult condition, the neural lobe is composed nearly entirely of neuroglia tissue. There are many long interlacing

fibres and scattered cells. There is no fibrous connective tissue, except around the larger blood-vessels and no nerves have been demonstrated with certainty. Between the neuroglia fibres are found rounded or irregularly-shaped bodies, which stain pink with eosin and which are called hyaline bodies. Their true nature is still undetermined. There are also coarsely-granular masses, which have been thought to be pigment, but this is undecided. A very active extract, **pituitrin,** is obtained from the pars nervosa and the pars intermedia. The secretion is formed by the cells of the pars

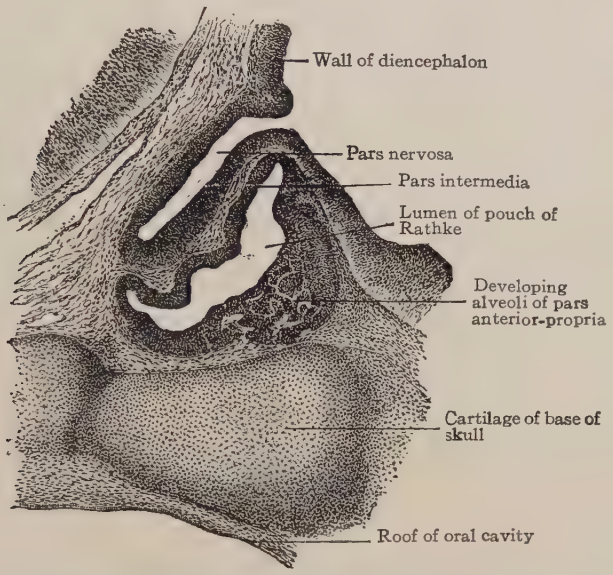


FIG. 243—Portion of sagittal section of rabbit embryo, showing developing hypophysis; alveoli are sprouting from wall of oral diverticulum. × 50.

intermedia, and then collected and concentrated in the pars nervosa. Part of the secretion passes up the infundibular stalk to enter the cerebrospinal fluid.

THE EPIPHYSIS CEREBRI

The pineal body, also called the **epiphysis** and the **conarium,** is a cone-shaped organ, from 8–10 mm. in length, attached to the posterior extremity of the roof of the third ventricle.

As seen in sections of the adult human organ, its structure includes a reticular framework of vascular connective tissue trabeculæ,the meshes of which are filled with rounded or elongated epithelial cells, which often contain brownish pigment. With the exception of a few nerve-fibres in the anterior part, probably sympathetic in origin and destined for the walls of the blood-vessels, and a dense network of neuroglia-fibres in the under part, the pineal body contains no elements of a nervous character, nerve-cells being absent. Very commonly the adult organ encloses a variable number of

concretions, called **brain-sand** or **acervulus cerebri,** which consist of laminated masses composed of calcium carbonate and phosphate, mingled with

FIG. 244—Section of epiphysis, showing general structure and calcareous concretions. × 130.

organic material. They may be of microscopic dimensions, or reach the size of a millet seed, and by aggregation assume a mammillated form.

THE CAROTID BODY

This organ, also known as the **glomus caroticum, carotid gland,** and **ganglion intercaroticum,** is a small ovoid body measuring usually about 5 mm. in length, from 2.5–4 mm. in width and about 1.5 mm. in thickness. It may attain a length of 7 mm. and exists on both sides. Its most frequent position is on the median and deep side of the upper end of the common carotid artery in close relation with the point of division of the latter vessel into the external and internal carotids. The body usually lies not within the bifurcation, but rather on the inner side of the common carotid, so that its form and relations are best displayed by dissection from within outwards.

The body is surrounded by a thin fibrous **capsule,** from which delicate septa penetrate inwards and divide the organ into a small and uncertain number (5–15) of spherical masses, or **lobules,** from .2–.5 mm. in diameter, which consist of a complex of blood-vessels, nerve-fibres, and peculiar cells. The latter are irregularly disposed as clumps, or cell-balls, and occupy the interspaces within the close network of large capillaries which ramify among the cells. The characteristic elements of the carotid body are the polygonal cells about 10 μ in diameter, with large round nuclei. Their protoplasm is finely granular and is especially prone to change, being best preserved in solutions of chromic acid salts. When so treated, they take on the peculiar

yellow color entitling them to be classed as **chromaffin cells.** The large number of nerve-fibres within the carotid body is remarkable. They are mostly unmyelinated and are derived chiefly from the neighboring sympathetic plexus surrounding the carotid artery. After entering at different places, they ramify within the organ in all directions, the finest filaments being lost among the groups of cells. The penetrating nerve-trunks usually enclose typical ganglion-cells and, in a sense, the chromaffin cells likewise, since the nerve-fibres surround the groups of these elements.

In view of (1) the identity of its elements with other chromaffin cells, which are now recognized as closely associated with the sympathetic system

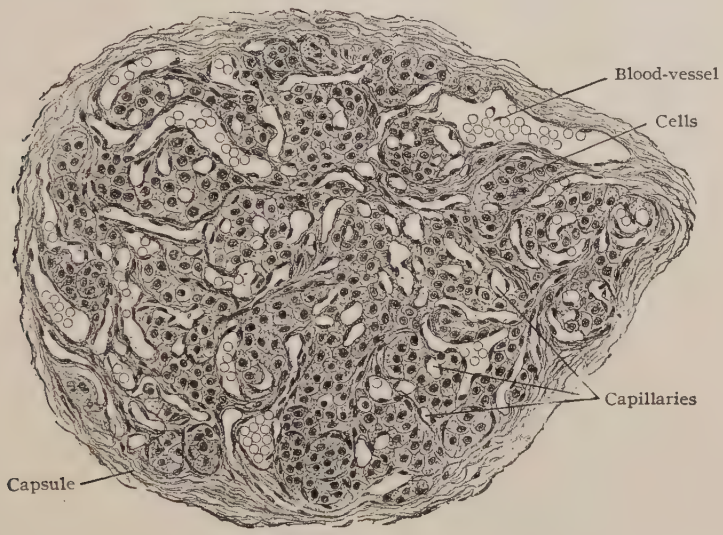


FIG. 245—Section of carotid body of adult man; one entire lobule is shown. × 170.

in other localities, as in the medulla of the adrenal body, (2) its extraordinary richness in nerve-fibres, (3) its general resemblance to a sympathetic ganglion, and (4) its early development from embryonal sympathetic ganglion-cells, Kohn concludes that, since the carotid body is neither a gland nor a typical ganglion, it must be regarded as accessory to the sympathetic system, and, in recognition of this relation, proposes the name **paraganglion caroticum** for the organ. Concerning its function nothing is definitely known; possibly this depends upon adrenalin from the chromaffin tissue.

The blood-vessels supplying the carotid body are branches which pass directly from either the common carotid artery or its terminal branches.

THE COCCYGEAL BODY

This organ, also often called the **glomus coccygeum, coccygeal gland,** or **Luschka's gland,** is a small, reddish-yellow, ovoid body which lies embedded in fatty areolar tissue usually immediately in front of the tip of the coccyx, but sometimes just below. The dimensions of the organ are small, its

transverse and greatest diameter being from 2.5–3 mm. and its thickness less than 2 mm. It sometimes is divided into two or even more tiny lobes. The body thus described is, however, only the largest of a series of nodules which include a variable number of structures, for the most part of minute size, irregularly grouped around the chief mass. The additional nodules are in many cases connected with the principal body by means of delicate pedicles; in others they are entirely free, but in all instances they are grouped around the middle sacral artery or its branches.

The body, as seen in transverse sections (Fig. 246), includes an irregularly oval field of connective tissue, fairly well defined from the surrounding fatty areolar tissue, in which are enclosed numerous aggregations of epithelial cells and, sometimes, a thick-walled artery. The proportion of cell-

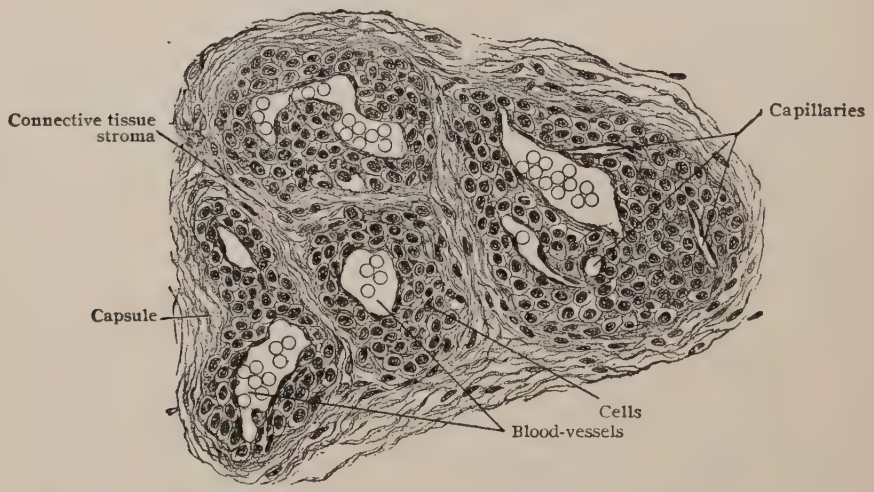


FIG. 246—Section of coccygeal body of adult man. × 220.

masses to the connective tissue stroma varies, in some cases the cellular constituents predominating, but commonly the fibrous stroma being the more bulky. The individual cell-groups are uncertainly circumscribed by a slight condensation of the surrounding fibrous stroma. Each aggregation of cells contains a central blood-space, limited by an endothelial wall similar to that of a capillary. Against this wall the epithelial cells lie without the intervention of connective tissue; likewise the cells themselves are closely packed in direct apposition with one another and in consequence present a polygonal contour. They are disposed around the central vessel in from two to five layers, the individual cells being indistinctly outlined and composed of clear protoplasm containing a relatively large and deeply-staining nucleus. Concerning the mooted question as to the presence of chromaffin cells within the coccygeal body, the testimony as to their absence seems convincing. The cells at no period exhibit the chrome-reaction, and have no histogenetic relation to the sympathetic system. On the other hand, the

epithelial character of the cells, their intimate relation to the blood-vessels, and the absence of excretory ducts, has suggested its inclusion as an organ of internal secretion; however, there is no final evidence as yet.

THE ISLET-CELLS OF THE PANCREAS

The internal secretion of the pancreas which is concerned with carbohydrate metabolism is derived from the islet-cells, and has been named insulin. As already mentioned under pancreas (p. 215), there are two types of granular cells (α and β) found in the islets by differential staining after suitable fixation (Lane, *Am. J. Anat.*, '07; Bensley, '11; Bowie, *Anat. Rec.*, '24). A third type of cell, showing no specific granulations (γ-cells), is also present and may represent a transitional stage between ductule-cells and the α- and β-cells. According to recent reports, there are evidences of regeneration of the islet-cells during insulin treatment of diabetic patients.

THE INTERSTITIAL CELLS OF TESTIS

Within the testes are produced, for the most part, the internal secretions which determine the secondary sexual characters. That these secretions are produced by the interstitial cells is the preponderating opinion at the present time, but the other tissues of the testis,—the Sertoli cells and the spermiogenetic tissues, may also contribute to them. The cells form, collectively, the interstitial gland of the testis. The groups of cells are found between the seminiferous tubules, and are often characterized by containing fine pigment granules. The cells are polyhedral in shape, and in them have been found centrosomes, fat, mitochondria, crystalloids and the internal reticular apparatus of Golgi, but as yet the specific secretory substance has not been demonstrated histologically.

THE LUTEAL TISSUE, VESICULAR FOLLICLES, AND INTERSTITIAL CELLS OF OVARY

The ovary contains three, or more, sources of internal secretion. The luteal tissue originates from the walls of the Graafian follicles, after ovulation, probably from both stratum granulosum and theca interna. The cells are large, polyhedral, and have a rich vascular supply. In these cells have been demonstrated centrosomes, neutral fat, lipoid, mitochondria and the internal reticular apparatus of Golgi, as well as pigment.

The liquor folliculi of the vesicular follicles contains an active hormone, which is probably produced through the activities of the follicular epithelium, or stratum granulosum lining the Graafian follicles. The structure of the latter is described later under Ovary (*q.v.*).

There is much uncertainty as to the presence and recognition of the interstitial cells in the adult human ovary. In a series of 43 pairs of ovaries, sectioned serially, only two ovaries, from different individuals, showed in the hilum a small island of cells identical in appearance with the interstitial cells of the testis (Lewin, '26). They have been studied chiefly in other mammals, as rabbit and cat. In their cytoplasm are found many lipoid droplets, which may contribute to the internal secretion of these cells.

THE ORGANS OF RESPIRATION

THE respiratory tract proper, that is excluding the nasal fossæ (through which the air passes when the mouth is closed) and the pharynx, includes the organs concerned in effecting the interchange of the gases between the blood and the inspired air and, in addition, the production of voice. It comprises the **larynx,** the **trachea** and its subdivisions, the **bronchi,** and the **lungs,** together with the serous membranes, the **pleuræ,** which surround the lungs and line the spaces containing them. The respiratory tract is developed as a ventral outgrowth from the primitive gut-tube and is lined, therefore, by entodermic epithelium, all other parts of the organs being derived from the mesoderm.

THE LARYNX

The larynx consists of a fibro-cartilaginous framework lined with mucous membrane and surrounded by muscles. By the action of the latter the relative position of the cartilages is modified, thereby effecting the approximation and tension of two folds of mucous membrane, known as the vocal folds that cover the free edges of fibro-elastic membranes and bound the cleft through which the air passes to and from the windpipe. In order to have clearly in mind the relations of the parts, it is advisable to examine a good dissection of or a model of the larynx.

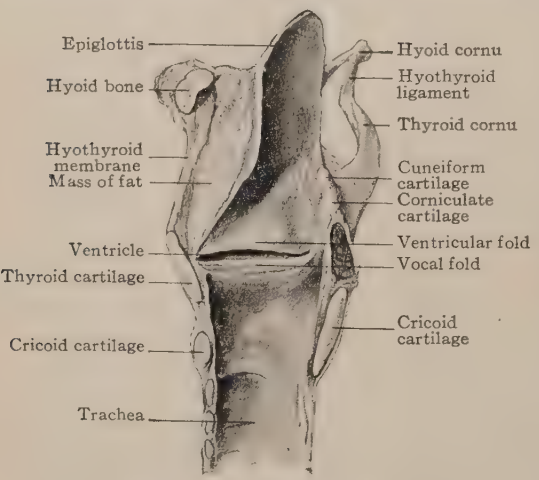


FIG. 247—Median sagittal section of larynx; right half, seen from within. × ¾.

The **cartilages** of the larynx include three single ones: the **cricoid,** the **thyroid,** and the **epiglottis;** and three paired ones: the **arytenoid,** the **corniculate,** and the **cuneiform,** the last being small and sometimes wanting. Other minute masses of cartilage will be noted in connection with the structures in which they occur. In structure the laryngeal cartilages correspond to the hyaline variety, with the exception of the epiglottis, the tip and vocal process of the arytenoid, the cuneiform, and the corniculate, which parts consist of elastic cartilage and seldom, if ever, exhibit replacement by bone. Beginning about the twentieth year, more or less extensive ossification of the cartilages, especially the thyroid and

cricoid, occurs as a normal change. The arytenoid cartilages are less affected and they remain unchanged in women much longer than in men.

The **mucous membrane** lining the larynx is a prolongation of that of the pharynx, and consists of the epithelium and tunica propria, with the underlying submucous tissue by which the mucosa is attached to the surrounding framework. The **epithelium** is, for the most part, stratified ciliated columnar except over the true vocal folds, as well as over the laryngeal surface of the epiglottis and the anterior aspect of the arytenoid cartilages, where the epithelium is of the stratified squamous variety. In this respect,

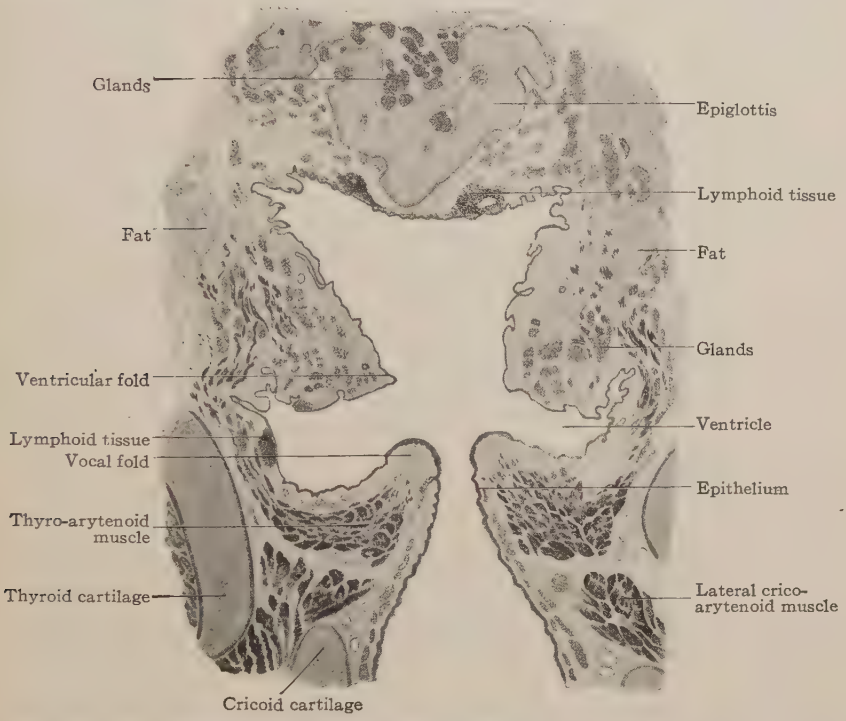


FIG. 248—Frontal section of larynx passing through epiglottis, vocal folds and ventricle; the plane of section is at right angles to that of preceding figure. × 2¾.

however, the mucosa of the upper half of the larynx presents many individual variations, since patches of squamous epithelium are often observed within the more general lining of columnar cells. Small scattered taste-buds are often seen in the epithelium covering the epiglottis. The **tunica propria** consists of closely packed bundles of fibrous tissue, with an abundance of elastic fibres. It contains many lymphoid cells which in certain locations, as over the epiglottis and especially in the ventricle of the larynx (the lateral diverticulum between the false and true vocal folds), are aggregated into distinct although small lymph-nodules (Fig. 248).

The **submucous layer,** composed of loosely disposed bundles of fibro-elastic tissue, varies in amount in different parts of the larynx, with

corresponding modifications in the intimacy of attachment of the mucous membrane to the surrounding structures. Thus, it is meagre over the free part and laryngeal surface of the epiglottis, the arytenoid, and lower part of the cricoid cartilages, in which positions the mucosa is closely attached. Over the true vocal folds, the submucosa is practically wanting. On the other hand in the aryepiglottic folds (which bound laterally the superior laryngeal orifice) and in the ventricle it is abundant with consequent mobility of the mucosa. The submucous layer contains many groups of small, mixed, mucous, tubo-alveolar **glands.** They occupy pits in the cartilage of the epiglottis, and are numerous and relatively large over the false vocal cords (**plicæ ventriculares**) and plentiful in the ventricles. They do not occur on the upper sur-

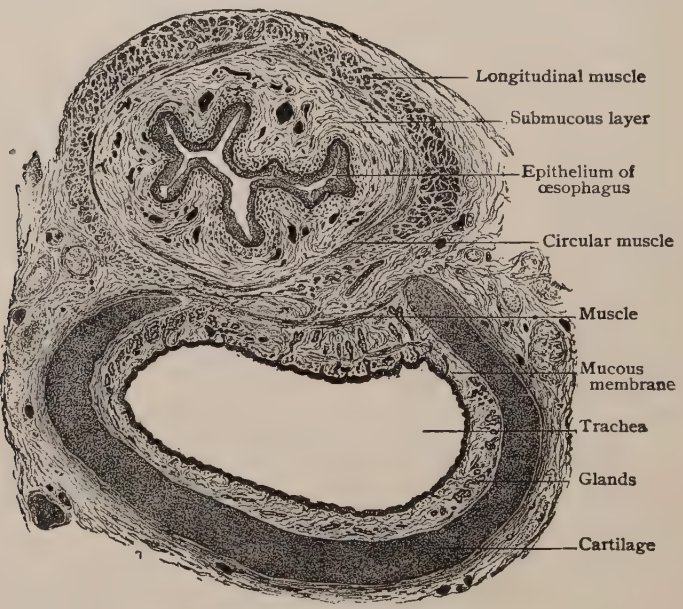


FIG. 249—Transverse section of trachea and œsophagus of child. × 15.

face of the true vocal cords within 3–4 mm. of their free margins, but beneath the latter the glands form almost a continuous layer.

The **vocal folds** (**plicæ vocales**), or **true vocal cords,** are two duplicatures of mucous membrane which cover the free median margins of the lateral crico-thyroid membranes. This part of the membrane, often designated the thyro-arytenoid ligament, is attached to the thyroid cartilage in front and to the vocal process of the mobile arytenoid cartilage behind, and is directly influenced by the contractions of the thyro-arytenoid muscle, which lies against the membrane externally and inserts many of its fibres directly into the fibrous band. The submucous tissue being wanting over the vocal cord, the here thin mucous membrane is intimately attached to the underlying fibrous stratum of the thyro-arytenoid ligament, thus insuring accurate response to the changes induced by muscular action. Small masses of

elastic cartilage, from 2–3 mm. long, are occasionally found in the anterior ends of the vocal cords; smaller pieces of similar tissue are quite common in the ventricular plicæ.

The numerous **blood-vessels** supplying the larynx are distributed chiefly to the mucous membrane, in which the main capillary network lies close beneath the epithelium. Other branches are given off within the submucous layer and provide the capillary supply for the numerous glands. The **lymphatics** are well represented throughout the greater part of the laryngeal mucous membrane, especially in the region of the ventricle and the false vocal folds. Over the true cord, however, they are very feebly developed, but below them the lymphatics are again numerous. Where abundant, the lymph-channels are present within the mucosa as a superficial and a deeper network, which communicate and pass to the cervical lymph-nodes.

The **nerves** supplying the larynx are chiefly from the vagi, intermingled with fibres from the sympathetic. They consist, therefore, of myelinated and unmyelinated fibres; groups of ganglion-cells occurring along the course of the sympathetic fibres. The latter are destined for the blood-vessels and glandular tissue. The muscles being of the striated variety are supplied by fibres bearing motor end-plates. The sensory fibres are distributed principally to the mucous membrane, in which they form plexuses. From the latter, unmyelinated fibres pass towards the free surface to terminate either in sub-epithelial end-arborizations bearing enlargements or end bulbs, or in intra-epithelial filaments ending free between the cells. Special end-organs have been described as existing within the true vocal cords.

THE TRACHEA AND BRONCHI

Beginning at the lower border of the cricoid cartilage, the trachea, or windpipe, extends into the thorax, a distance of some 10–12 cm., and divides into two bronchi, one proceeding downwards and outwards into each lung. Until the latter is reached, the walls of the air-tubes are constant in structure and consist essentially of a fibro-cartilaginous framework, lined with mucous membrane and covered externally with areolar tissue.

The cartilage is represented by a series of from sixteen to twenty C-shaped pieces, of the hyaline variety and from 2–5 mm. in width, which are united with one another by a fibro-elastic sheath continuous with the perichondrium of the segments. This membrane likewise connects the ends of the "rings", as the pieces are called, and thus completes the tube behind, where otherwise the framework of the posterior wall of the trachea and bronchi would be deficient. In order to maintain the proper tonicity of the fibro-cartilaginous tube, especially of its membranous portion, bundles of unstriped muscle, the **trachealis muscle,** lie between the ends of the cartilages. In the main these bundles are disposed circularly, connecting the ends of the cartilaginous rings.

The **mucous membrane,** smooth and attached with considerable firmness to the cartilages by the submucous tissue, but looser and thrown into longitudinal folds over the posterior wall, is clothed with stratified ciliated

columnar **epithelium.** Many of the surface cells contain mucus and are of the goblet variety. The **tunica propria** is rich in elastic fibres and contains numerous lymphoid cells, which are so abundant in places, particularly around the openings of the tracheal glands, as to suggest lymph-nodules. The **submucous layer,** composed of fibro-elastic tissue, lodges, in addition to the larger blood-vessels and lymphatics, the **tracheo-bronchial glands.** These occur as considerable masses (Fig. 250) and belong to the mixed,

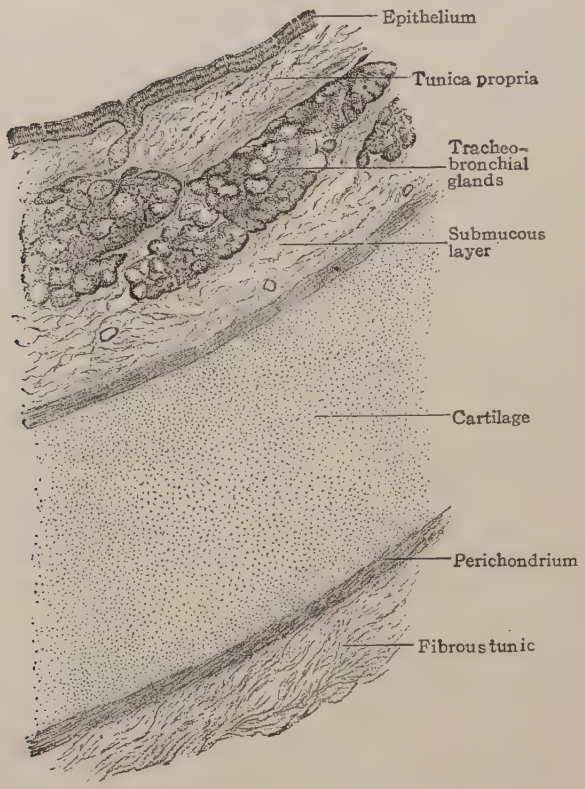


FIG. 250—Transverse section of trachea, showing general arrangement of the coats. × 80.

mucous tubo-alveolar type. Their ducts pierce the tunica propria and open on the free surface by minute funnel-like depressions in the epithelium. The blood-vessels, lymphatics, and nerves follow essentially the same plan of distribution as described in connection with the larynx.

THE LUNGS

In their mode of development and architecture, the lungs resemble compound alveolar, or saccular, glands, the repeatedly subdividing air-tubes (the bronchioles) representing the duct-system of a gland and the ultimate compartments of the respiratory tissue (the alveoli) corresponding to the

glandular alveoli. Before birth, the resemblance to glandular tissue is very striking, the alveoli being lined with cuboidal epithelium (Fig. 256), but after birth the alveoli are distended with air, and the lining epithelium is expanded into extremely thin cells.

The Lobule and Lung-Units.—The surface of the lung (Fig. 251), is marked with small polygonal areas, 10–25 mm. in diameter, which are defined by lines of connective tissue, often darkened by pigment. These areas are the bases of pyramidal masses of pulmonary tissue, the **lobules,** each of which is entered by and surrounds a minute air-tube, **intralobular bronchiole,** from .5–1 mm. in diameter, accompanied by a branch of the pulmonary artery. The bronchiole enters the lobule near its apex and divides into two a little above the middle of the lobule, having previously given off two or three collateral branches to its upper part. In the third quarter of the lobule the two branches subdivide in a plane at right angles to the preceding splitting. Such division is repeated in three or four successive bifurcations, a varying number of collaterals being given off in addition. Although the number of branches of the air-tubules is much increased in the third quarter, it is in the last one and towards the periphery of the lobule throughout that the tubules break up into a profusion (50–100) of truly **terminal bronchioles.** Each terminal bronchiole communicates by its slightly dilated distal extremity with from three to six spherical cavities, the **atria**, each of which, in turn, communicates with a group of larger irregular cavities, the **alveolar sacs,** into which directly open the ultimate air-spaces, the **pulmonary alveoli.** There are also scattered alveoli upon the distal parts of the terminal bronchioles and upon the walls of the atria. The mass of pulmonary tissue connected with each terminal bronchiole, including the air-spaces and accompanying blood-vessels and nerves, constitutes a **lung-unit** by the aggregation of which the **lobule** is formed. The lobules are separated by distinct tracts of interlobular connective tissue, in which the air-tubes and accompanying blood-vessels course until they enter the lobules.

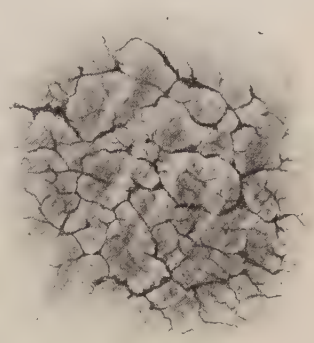


FIG. 251—External surface of lung, showing polygonal areas, corresponding to the lobules, mapped out by pigment within the connective tissue.

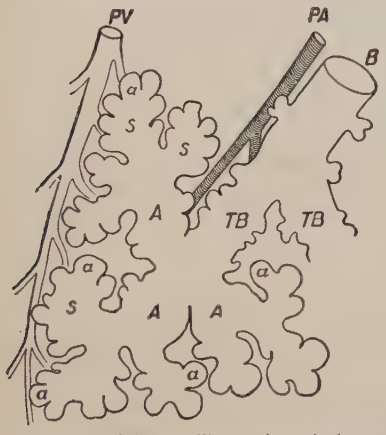


FIG. 252—Diagram illustrating relations of terminal divisions of air-tubes. *A*, bronchiole ending in terminal bronchi (*TB*): latter divide into atria (*A*), each of which communicates with several air-sacs (*s*) into which open the alveoli (*a*); *PA*, branch of pulmonary artery following bronchiole; *PV*, pulmonary vein at periphery of lung-unit: (*Miller.*)

The Bronchioles.—After the bronchus begins to give off branches within the lung, the cartilage-rings gradually decrease in size and thickness until replaced by irregular angular plates, which appear at increasingly longer intervals until they finally cease, cartilage being seldom present in bronchioles of less than 1 mm. in diameter. As the cartilage tends to disappear, the unstriped muscle broadens into a continuous layer, which, in turn, becomes thinner as the air-tube diminishes and extends only as far as the terminal bronchioles. The muscle is arranged as a sphincter-like band around the openings by which the terminal bronchioles communicate with the atria.

The walls of **bronchioles of medium size** (2–3 mm.) consist of three

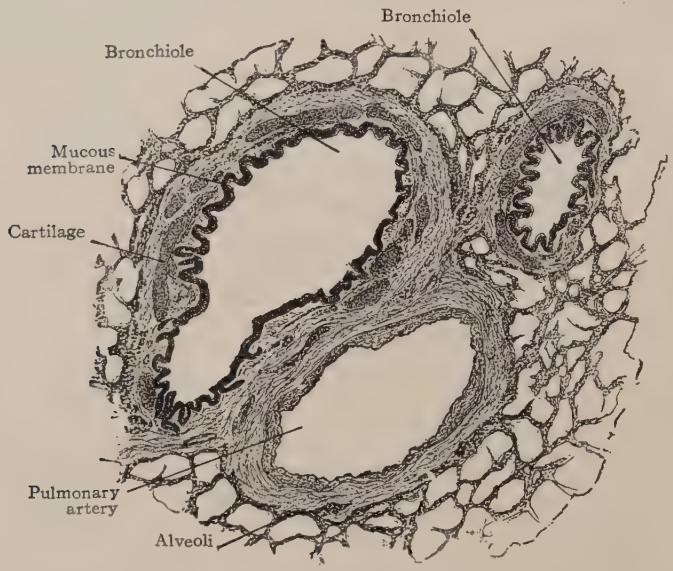


FIG. 253—Section of lung, showing small air-tubes and branch of pulmonary artery. × 35.

coats, which from without in are: (1) an external **fibrous tunic,** composed of fibro-elastic tissue, which encloses the cartilage (often elastic in type) and accompanying blood-vessels and blends with the adjoining lung-tissue; (2) a thin layer of **unstriped muscle,** sometimes incomplete and composed of circularly-disposed bundles; and (3) the **mucous membrane,** thrown into longitudinal folds and consisting of ciliated columnar epithelium, with numerous goblet-cells, and a tunica propria made up chiefly of meshes of elastic fibres and intervening lymphoid cells. As in the trachea and the bronchi, the current produced by the cilia is directed centrally and thus tends to carry mucus and particles of dust from the smaller tubes towards the bronchi and trachea. Mucous **glands,** similar to those of the trachea, are present in decreasing number and size until the bronchiole attains a diameter of 1 mm. after which they usually disappear. Their chief location is outside the muscle which is pierced by the ducts on their journey to gain the free

surface where they open in minute depressions within the epithelium. In addition to the lymphoid cells diffused through the mucosa, more definite aggregations occur as minute **lymph-nodules** along the bronchi, the points of bifurcation being their favorite seats. The epithelium lining the air-tubes retains the ciliated columnar type as far as the smaller bronchioles. Within the latter the ciliated cells are replaced by simple columnar elements, which, in turn, give way to low cuboidal cells within the proximal part of the terminal bronchioles. Towards the distal ends of the latter partial transition into patches of simple squamous epithelium occurs, these tubules containing, therefore, both cuboidal and plate-like cells.

The Terminal Air-Spaces.—The walls of the terminal air-spaces—the atria, the alveolar sacs, and the pulmonary alveoli—have essentially the

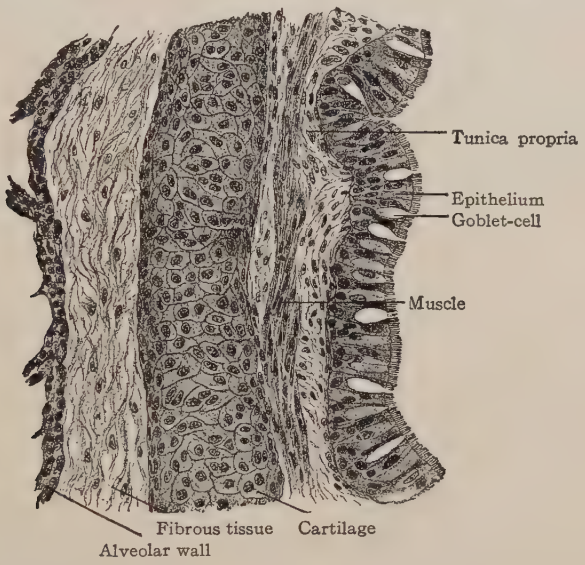


FIG. 254—Portion of wall of small bronchus. × 180.

same structure and consist of a delicate fibro-elastic framework supporting the blood-vessels and the epithelium. The latter, the **respiratory epithelium,** is made up of a single layer of extremely thin squamous epithelial cells, all of which are nucleated. The outlines of these plate-like cells are best seen in silvered preparations of the lung. In thin sections, some of these plates may not show a nucleus, but every apparently non-nucleated plate has really a nucleus as may be demonstrated in serial sections (Miller). In the fetus and in the still-born child, the alveoli are lined entirely by low cuboidal cells; during inflation of the lung-tissue the cuboidal cells become expanded into the thin plate-like cells.

The **framework** of the pulmonary alveoli is almost exclusively elastic fibres that are condensed into rings around the openings or bases of the alveoli and elsewhere enclose the spaces with elastic networks. Where these rings come into contact and fuse, the alveoli are separated by partitions of

some thickness; beyond these septa the walls between the adjoining air-spaces are very thin and include the two layers of epithelial cells and the dense capillary network supported by the elastic reticulum. Owing to the elastic character of their walls, the alveoli expand during inspiration to two or three times their usual diameter (.1–.3 mm.), the lining epithelial plates and the blood-vessels stretching to the necessary degree. The **capillary networks** surrounding the alveoli are in many places common to the opposed spaces belonging to the same unit. These networks, the terminations of the pulmonary artery and the beginnings of the pulmonary veins, possess exceedingly small meshes, the distance between the capillaries often being less than the diameter of the vessels. The latter, not confined, to one plane

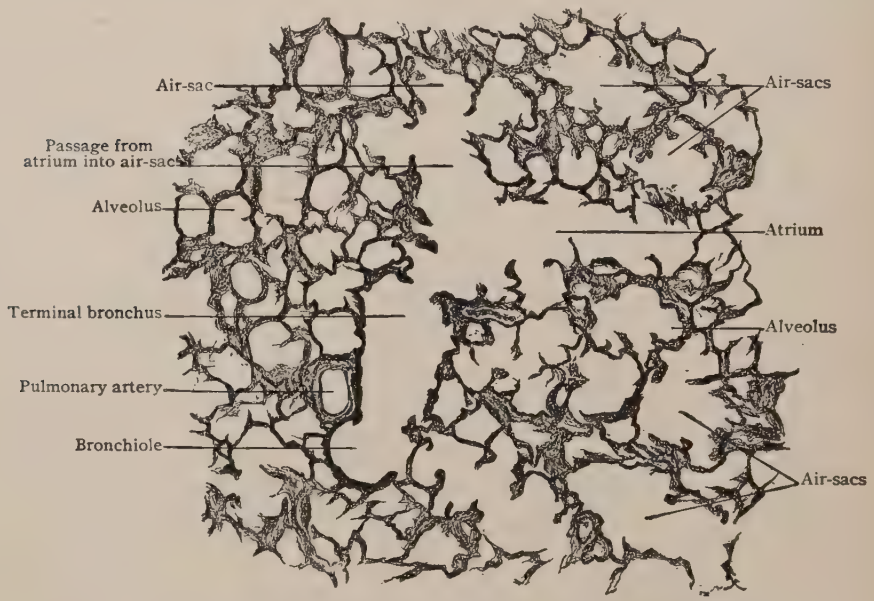


FIG. 255—Section of lung, showing relations of terminal divisions of air-tubes. × 50.

but sinuous, are excluded from the interior of the alveoli by practically only the thin layer of respiratory epithelium, an arrangement manifestly advantageous in effecting the interchange between the carbon dioxide of the venous blood and the oxygen of the inspired air.

Although preformed openings, or stomata, do not exist between the alveolar epithelial elements, particles of foreign materials pass through the wall of the air-spaces and eventually into the interlobular connective tissue, where they accumulate as the more or less conspicuous collections of pigment which aid in defining the outlines of the lobules. A certain amount of such pigmentation is always found in adult lungs and may be regarded as normal; when, however, individuals are subjected to an atmosphere unduly laded with colored particles, as coal dust, the pulmonary tissue may be so filled with pigment as to be in places almost black. It is probable that

migratory phagocytic cells are an important means of transporting the colored particles from the alveoli into the connective tissue.

The **blood-vessels** of the lung, as those of the liver, include two sets, the larger venous and the smaller arterial. The former are the branches of the pulmonary artery; the latter are the bronchial vessels. The bronchial arteries arise from the aorta, not directly from the heart. The branches of the **pulmonary artery** follow closely the ramifications of the air-tubes, entering the lobules near their apices, along with the intralobular bronchioles, and finally breaking up into the close capillary networks in the walls of the alveoli. From these networks arise the radicles of the **pulmonary veins** which carry away the oxygen-renewed blood. These vessels, however, do not immediately join the arteries, but, running first on the

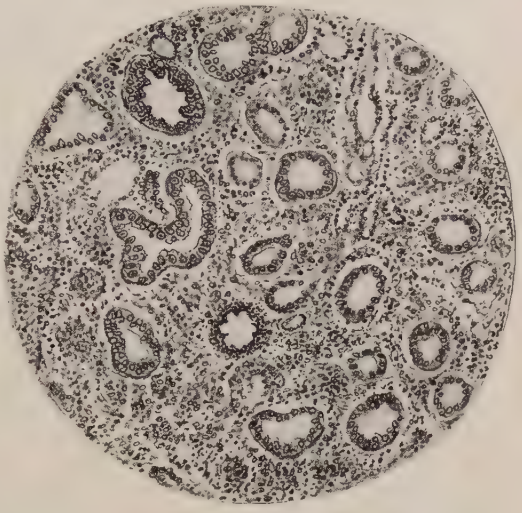


FIG. 256—Fetal lung, from 8-month fetus. Alveoli lined with cubical epithelium; lumina of bronchioles with stellate outlines; framework tissue abundant. × 90.

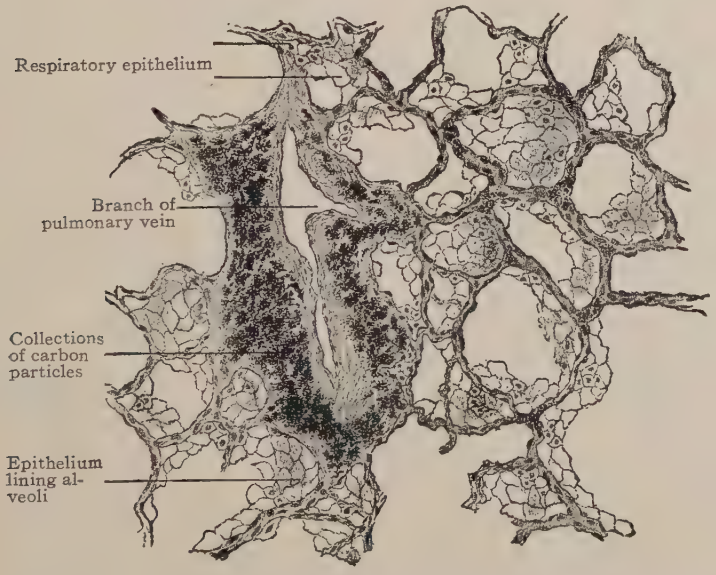


FIG. 257—Section of lung, showing alveolar epithelium and collections of colored particles in lymphoid tissue. × 140.

outside of the lung-units, unite with others and then emerge at the periphery of the lobules and run in the interlobular connective tissue, later meeting the interlobular parts of the arteries and bronchi which they thence accompany to the hilum of the lung. At the surface, where the pulmonary tissue is in contact with the overlying serous membrane, twigs from the pulmonary artery communicate with the pleural capillaries. The **bronchial arteries** supply the walls of the air-tubes as far as the terminal bronchioles, as well as the walls of the branches of the pulmonary artery and veins, the bronchial lymph-nodes and the visceral pleura. Within the walls of the bronchial tubes they form a deeper capillary network for the muscle and glands and a superficial one for the tunica propria. The **bronchial veins** are tributary for the most part to the pulmonary veins; to a small extent, however,

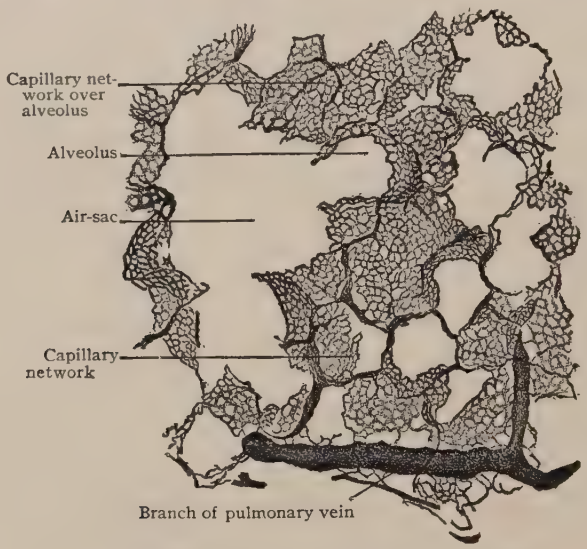


FIG. 258—Section of injected and inflated lung. × 80.

blood passes from them into the azygos system. Both the bronchial arteries and veins communicate with the pulmonary vessels at many points.

The **lymphatics** include a superficial network, well developed and beneath the pleura, and a deep interlobular plexus surrounding the bronchi. The deep ones probably begin as tissue-spaces distal to the terminal bronchioles, around which tubules definite lymphatics first appear. The superficial vessels are connected with small, uncertain, subserous lymph-nodes, subsequently joining the interlobular trunks, which ultimately are efferent to the larger nodes situated in the hilum and roots of the lungs. The pulmonary lymph-nodes are deeply pigmented owing to the accumulation of inspired dust particles. Where cartilage exists, the plates are enclosed by double networks of lymphatics, the inner one lying within the submucosa.

The **nerves** of the lungs, from the vagi and sympathetics, are numerous and include both myelinated and unmyelinated fibres. The latter are

associated with minute groups of ganglion-cells along their course and are destined chiefly for the walls of the blood-vessels and of the air-tubes, some fibres finding their way into the interalveolar septa. Free terminal filaments within the tunica propria and between the epithelial cells are described as sensory endings in the mucous membrane of the air-tubes.

The Pleuræ.—The pleuræ, the serous membranes lining the cavities containing the lungs and covering the latter except at the roots where enter the bronchi and the blood-vessels, in structure closely resemble other serous membranes. The visceral pleura consists of a **stroma-layer,** composed of fibrous tissue intermingled with an abundance of elastic fibres, and a single surface layer of **mesothelial plates.** The parietal pleura possesses a like structure, but is less rich in elastic fibres. The **subserous layer** is scanty over the lung, where it is continuous with the interlobular connective tissue; over the mediastinum it is firm and dense and on the costal wall acquires the character of a fascia, which is particularly dense beneath the apical pleura.

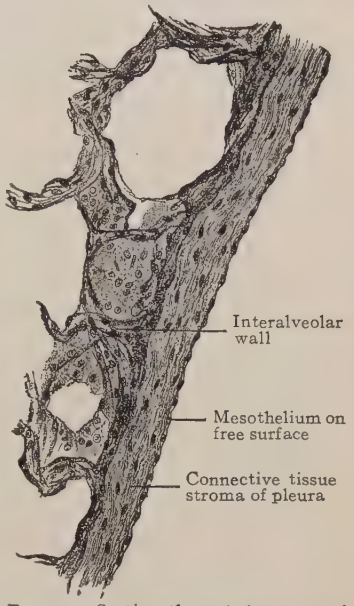


FIG. 259—Section through free edge of lung, showing visceral pleura. × 150.

The **blood-vessels** supplying the visceral pleura are derivations of the pulmonary trunks; those of the parietal pleura are from various adjacent systemic branches. In neither case is the ultimate distribution a generous one, the twigs being small and the capillaries comparatively few. The **lymphatics** are most abundant over the lungs and the intercostal spaces, where they form networks within the stroma and the subserous tissue. The **nerves** of the visceral pleura include fibres from the vagi and sympathetics by way of the pulmonary plexuses. Those of the parietal pleura receive fibres from the intercostal and phrenic nerves and, additionally, some from the vagi and the sympathetics. Many of the sensory fibres are connected with special end-organs, as the Pacinian and Golgi-Mazzonian corpuscles, while others terminate in free varicose endings.

THE URINARY ORGANS

THESE organs include the **kidneys,** the glands which secrete the urine, the **ureters,** the canals which collect the urine and convey it from the kidneys to the **bladder,** the receptacle in which the urine is temporarily stored, and the **urethra,** the passage through which the urine is discharged.

THE KIDNEYS

The kidneys are two flattened ovoid glands, of distinctive bean-shaped form, deeply placed within the abdominal cavity against its posterior walls, one on each side of the lumbar spine. They are invested by a thin **fibrous capsule,** which is distinct from the renal tissue beneath, and which may be easily stripped off in the normal fresh kidney. The mesial concave border of each kidney is interrupted by a slit-like opening, the **hilum,** which leads into a more extended but flattened space, the **sinus,** enclosed by the surrounding substance of the kidney. In addition to the blood-vessels, lymphatics, and nerves passing to and from the kidney through the hilum, the sinus contains the upper expanded end of the ureter, which also emerges at the hilum. The interspaces between these structures are filled with loose fatty areolar tissue.

FIG. 260—Kidney of new-born child, showing areas on surface corresponding to primary lobes.

Architecture of the Kidney.—The entire organ—a conspicuous example of a compound tubular gland—is made up of a number of divisions which in the mature condition are so closely blended as to give little evidence of the striking subdivision of the fetal kidney. The external surface of the latter (Fig. 260), is broken up by furrows into a number of polygonal areas, each of which represents the base of a pyramidal mass of renal substance, the **kidney lobe,** separated from its neighbors by connective tissue. It includes the entire thickness of the organ, between the exterior and the sinus, and ends internally in a conical apical projection, the **renal papilla.** Shortly after birth, the lobation gradually disappears on the surface, which becomes smooth, the interlobar connective tissue septa within the organ likewise disappearing, while the papillæ alone remain as indications of the original subdivisions. Although the outlines of the lobes occasionally persist on the surface of the adult human kidney, in many of the lower animals (reptiles, birds, ruminants, cetaceans, and certain carnivora) the subdivisions are normally retained. In some mammals (rodents and insectivora) the entire kidney corresponds to a single papilla, while in others (elephant and horse) no distinct papillæ exist.

On examining the cut surface of the kidney, opened by a longitudinal section passing from the convex border through the sinus (Fig. 261), the papillæ are seen to form the free apices of conical areas, the **renal pyramids,**

whose bases lie embedded within the surrounding kidney-substance composing the outer third of the organ. This peripheral zone, which in the fresh kidney appears darker and granular when compared with the lighter and striated renal pyramid, is the **cortex.** The **medulla** includes the conical areas of the pyramids and partially occupies the inner two thirds of the thickness of the organ. The cortex constitutes about two thirds of the volume of the kidney, forming the entire surface, including the lips of the hilum, and receiving and surrounding the bases of the pyramids. The cortical tissue, further, penetrates between the pyramids, separating them and in places gaining the sinus. These interpyramidal extensions are the **renal columns,** or **columns of Bertin,** and consist of typical cortical substance. Since the branches of the renal blood-vessels lie within the interlobar connective tissue separating the primary subdivisions of the fetal organ, these vessels never enter the kidney-substance by passing into the papillæ, but always at the side of and between these. They sink into the renal substance therefore, through the areas occupied by the renal columns, the free surfaces of which are pitted by the vascular foramina.

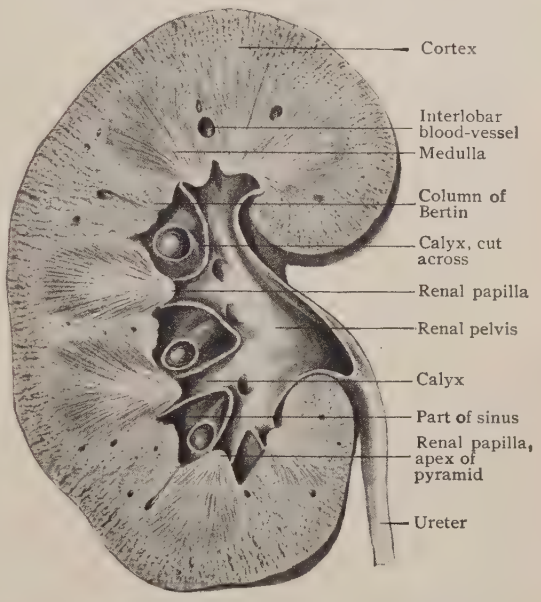


FIG. 261—Longitudinal section of kidney, showing divisions of renal substance and relations of pelvis and calyces.

On inspection with a magnifying glass, it will be seen that the cortex is not uniform, but is subdivided into radially-disposed darker and lighter tracts. The latter, longitudinally striated and wedge-shaped, are the **medullary rays,** or **pars radiata,** since they are apparently continuations of the medullary tissue. The darker tracts, between the medullary rays, constitute the **labyrinth,**[1] or **pars convoluta,** and appear granular owing to the tortuous course of the component uriniferous tubules. The labyrinth is studded with bright red points marking the position of minute vascular tufts, or **glomeruli;** these are limited to the labyrinth and, therefore, never present within the medullary rays or the renal pyramids, although found within the column of Bertin.

On sectioning organs in which the blood-vessels have been injected, it will be observed that the larger interlobar arteries, on gaining the boundary zone between the cortex and the medulla, break up into smaller branches, some of which pass towards the surface, while others change their direction

and assume a more horizontal course. Those running perpendicular to the exterior of the kidney occupy the centres of the labyrinth tracts and give off the afferent vessels to the glomeruli.

The Kidney-Substance.—The fundamental components include: (1) a tuft of arterial capillaries derived more or less directly from the aorta through the renal artery and its branches; (2) tubules lined with epithelium;

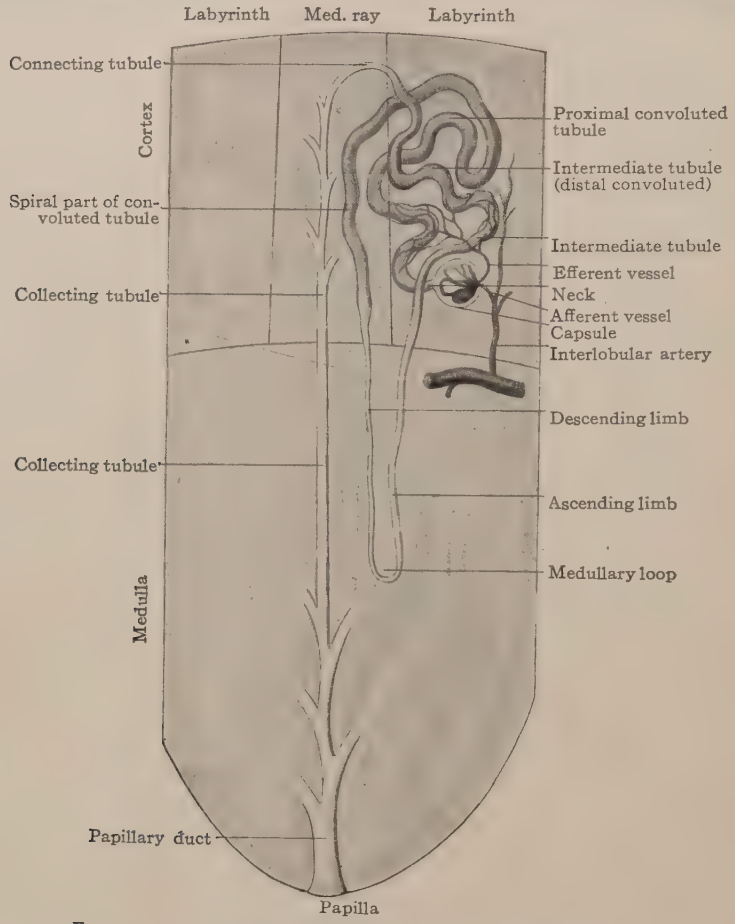


FIG. 262—Diagram illustrating the course of a uriniferous tubule.

and (3) a duct for conveying the excretory products. These constituents are, respectively: (1) the **glomerulus,** (2) the convoluted **uriniferous tubules,** and (3) the collecting tubules and the ureter composing the **duct-system.** The kidney-substance consists of an intricate, although definitely arranged, complex of uriniferous tubules, supported by an interstitial connective tissue stroma, which have their commencement in the cortex and their termination at the apices of the papillæ, their intervening course being marked by many and conspicuous variations in the character, size, and direction of the

tubules. It has been computed that there are 1,040,000 glomeruli, in each human kidney (Kittelson, '17).

The **uriniferous tubule** begins as a greatly expanded blind extremity, the **capsule,** (1), which has been invaginated into a double-walled cup by the pressing-in during development of a vascular tuft, or **glomerulus.** The two together constitute a **renal corpuscle**, or **Malpighian body,** which lies within the labyrinth. On leaving the renal corpuscle, the tubule becomes very tortuous and arches towards the free surfaces as the **proximal convoluted tubule** (2); this, after a course of considerable length, usually leaves the labyrinth and enters the medullary ray, which it traverses, somewhat reduced in diameter and slightly winding in course, and from this latter fact, is often called the **spiral part** of the proximal convoluted tubule. Immediately upon gaining the medulla, the tubule becomes markedly narrowed, penetrates the renal pyramid for a variable distance towards the papilla, then bends sharply upon itself and retraces its course to enter once more the labyrinth. Its excursion into the medulla includes the **descending limb** (3) and **ascending limb** (4) of the **medullary loop,** or **loop of Henle.** The ascending limb —the longer and wider of the parallel limbs of the loop—rises within the labyrinth to the immediate vicinity of the corresponding renal corpuscle and then, after arching over or around the body, gives place to the **distal convoluted tubule** (5), a segment which, marked by increased diameter and tortuosity, crosses the general path of the proximal convoluted tubule and is succeeded by the narrower arching **connecting tubule** (6). The latter soon enters the medullary ray and joining with similar canals takes part in forming

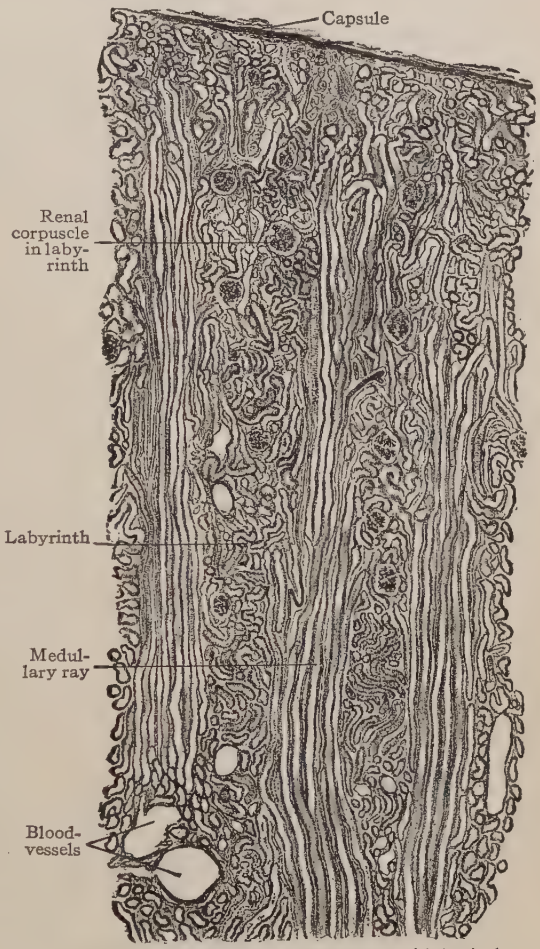


FIG. 263—Section of cortex, showing relation of labyrinth to medullary rays. × 50.

the straight **collecting tubule** (7), which, progressively increasing in size by junction with others, traverses the remaining length of the medullary ray and enters the pyramid. Within the deeper part of the latter, the collecting tubules fuse into larger and larger canals until, as the relatively wide **papillary ducts** (8), they terminate at the apex of the papilla at the orifices, the **papillary foramina,** which open into the **calyces,** as the subdivisions of the expanded beginning of the renal duct are called.

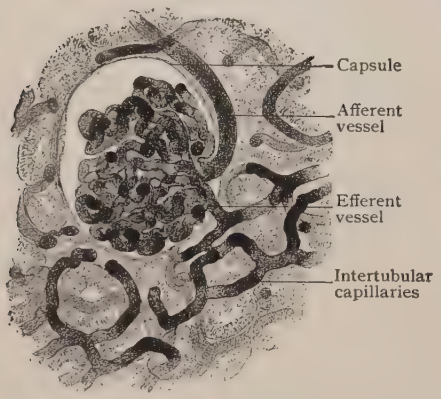


FIG. 264—Injected glomerulus, showing afferent and efferent vessels and continuation of the latter into the intertubular capillary network. × 180.

Although as a matter of convenience the entire canal, from its commencement at the renal corpuscle to its termination on the papilla, has been described as the uriniferous tubule, both genetically and functionally two distinct parts should be recognized. These are (**a**) the **uriniferous tubule proper** which includes all the conventional subdivisions from the Malpighian body to the termination of the distal convoluted tubule; and (**b**) the **duct-tube,** which, when traced from the papilla towards the cortex, undergoes

FIG. 265—Section of cortex, showing details of a renal corpuscle, or Malpighian body; the glomerulus is surrounded by capsule which passes into obliquely cut neck of tubule. × 200.

repeated division until, from the single main stem, the number of connecting tubules is sufficient to provide each uriniferous tubule proper with an excretory canal.

Details of the Uriniferous Tubule.—The general course and relations of the tubule having been sketched, a brief account of its more important structural details may here find an appropriate place.

1. The **renal corpuscle,** or **Malpighian body,** irregularly spherical and from .12–.20

FIG. 266—Convoluted tubules, cut transversely and obliquely, showing character of epithelial lining. × 280.

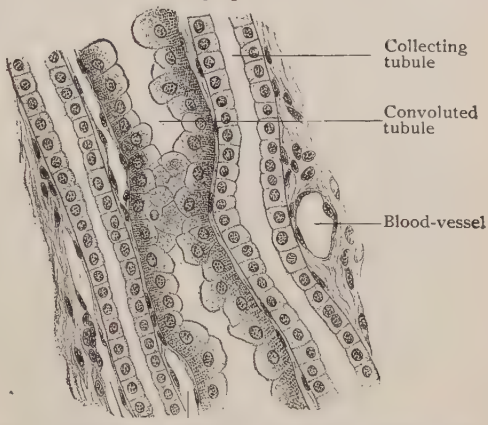


FIG. 267—Portion of medullary ray, showing "spiral" part of convoluted and collecting tubules. × 280.

mm. in diameter, consists of the glomerulus and the capsule. The **glomerulus** is an aggregation of tortuous capillary blood-vessels derived from the lateral branches of the cortical arteries as these traverse the labyrinth-areas towards the free surface of the kidney. One of the lateral branches, very short and often arched, enters the adjacent renal cor-

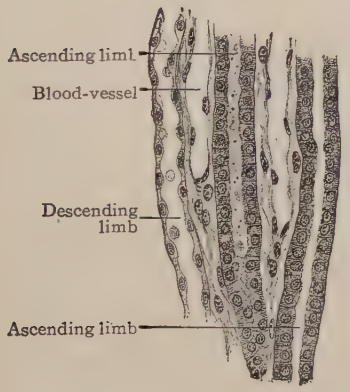


FIG. 268—Longitudinal section of medulla, showing parts of limbs of medullary loop. × 280.

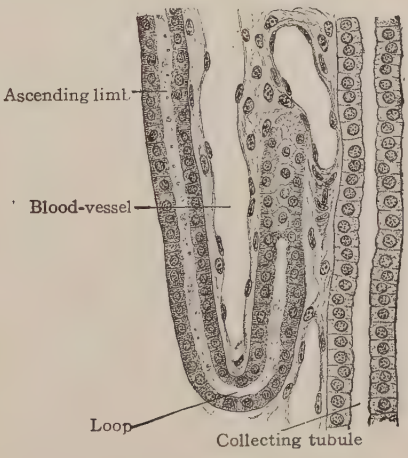


FIG. 269—Longitudinal section of medulla passing through medullary loop. × 280.

puscle as the **vas afferens,** where it divides into from four to six twigs, each of which breaks up into capillaries. These may anastomose and form a vascular complex, or each terminal twig may give rise to an isolated capillary territory, the entire glomerulus then consisting of a group of vascular lobules. The channels of exit unite to form the single **vas efferens,** through which the blood from the glomerulus escapes. The **capsule,** the invaginated dilated beginning of the uriniferous tubule, by reason of its mode of formation

almost completely invests the glomerulus with a double layer. The outer and inner layers are continuous around the margin of the narrow opening through which the vessels pass to and from the glomerulus. The inner ("visceral") layer is firmly attached to the glomerulus by delicate strands of connective tissue which likewise holds together the capillaries and follows the irregularities of the outer surface of the capillary lobules. As a result, its flat epithelial cells are not so readily distinguished as those of the outer layer of the capsule. The outer layer of the capsule consists of a membrana propria lined with a single layer of flat epithelial cells, directly continuous with the epithelium of the tubule.

FIG. 270—Longitudinal section of renal pyramid, showing general structure of medulla with medullary loops and collecting tubules. × 45.

2. The **proximal convoluted portion** begins at the constriction, the **neck,** of the capsule and abruptly widens into the tortuous segment that forms approximately one fifth of the entire length of the tubule. Its diameter varies from 40–60 μ. In common with other parts of the renal tubule, its wall consists of a homogeneous basement membrane lined with a single layer of epithelial cells. The latter, in the convoluted tubule, are not defined by sharp outlines, but the spherical nuclei which lie near the basement membrane, indicate the approximate extent of the individual low columnar cells. Although subject to much and inconstant variation, their cytoplasm exhibits a differentiation into a broad darker **outer** and a narrow lighter **inner zone.** The former is marked by coarse radial striations, the so-called rods, produced by parallel rows of granules. The narrow inner zone, next the lumen, is relatively clear, containing few granules and showing a faint striation. This "bristle border," as it is sometimes called, is seen only in very well preserved tissue; since it is prone to disintegrate, the partially destroyed border may give rise to appearances mistaken for cilia. During active secretion, the epithelial cells are relatively low and the lumen of the tubule is wide, these relations being reversed during periods of functional inactivity.

3. The **medullary loop,** or **loop of Henle,** begins in the boundary zone between the cortex and medulla by the passage of the spiral segment of the convoluted tubule into the **descending limb,** which is distinguished not only by the conspicuous reduction in its diameter (12–15 μ), being the narrowest part of the entire renal tubule, but also by the character of its epithelium. The latter consists of low flattened elements, in which the ellipsoidal nuclei equal or surpass the thickness of the cells, whose cytoplasm is clear or slightly granular. The **ascending limb** differs from the descending in its increased diameter (24–28 μ), thicker epithelium, which is dark and striated, and extension into the cortex. Since the cuboidal cells are often irregular in height, the lumen correspondingly

varies, in places being almost obliterated. The position of the medullary loop is influenced by the level of the corresponding renal corpuscle within the cortex—the nearer the medulla its corpuscle lies, the greater the descent of the loop towards the papilla, and **vice versa.** On entering the cortex the ascending limb rises to the immediate vicinity of its renal corpuscle, around or over which it curves to end in the succeeding distal convoluted tubule. The usual position of the sudden transition from the narrow into the wider part of the medullary loop is in the descending limb a short distance above the loop, although the change may occur beyond the turn or even within the bend itself.

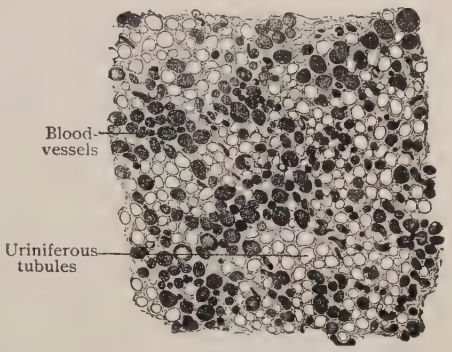


FIG. 271—Section across upper part of renal pyramid, showing groups of blood-vessels surrounded by uriniferous tubules. × 50.

4. The **distal convoluted, or intermediate portion,** from 40-45 μ in diameter, pursues a moderately tortuous path, marked by a number of abrupt changes in direction, but in a general way is enclosed by the arch of the proximal convoluted segment which it finally crosses. Its epithelium, which at first resembles that of the ascending limb, becomes clearer and less distinctly striated, the cells having a more definitely defined low cylindrical or pyramidal form although presenting local variations in height.

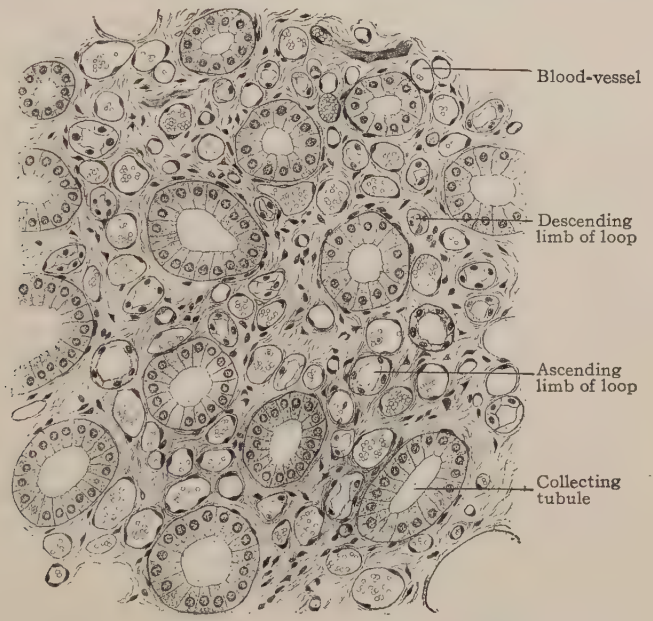


FIG. 272—Section of medulla across renal pyramid, showing large collecting tubules, limbs of medullary loops, blood-vessels and intertubular stroma. × 130.

5. The **connecting,** or **junctional, portion,** effects the union of the uriniferous tubule proper with the duct-system. It is narrower (23–25 μ) than the preceding segment and lined with well defined cuboidal cells, which being lower afford an increased lumen. After a short and somewhat arched course, the connecting tubule enters the medullary ray and, uniting with similar canals, joins in forming the collecting tubule.

6. The **collecting tubule** at first lies within the medullary ray and then passes into the renal pyramid. During their course through the medullary ray, the collecting tubules repeatedly unite to produce stems, which, while increasing four- or five-fold in diameter, diminish in number as they descend in the medulla. In consequence of this fusion, within the pyramid the collecting tubules are disposed in groups, each of which corresponds to the tubules prolonged from a single medullary ray, surrounded by the limbs of the medullary loops. The groups are further separated by the bundles of straight blood-vessels (**vasa rectæ**) of the medulla. The epithelium lining the collecting tubules consists of clear, distinctly defined, cuboidal cells, whose height gradually increases as the medulla is traversed. After converging to within about 5 mm. of the apex of the papilla, the now large collecting tubules undergo repeated junction, increasing in diameter (50–60 μ), but rapidly diminishing in number to form the wide papillary ducts.

7. The **papillary ducts** the final segment of the renal tubule, number from ten to eighteen for each papilla, at the apex of which they open into the calyx. Each is formed by the junction of from ten to thirty of the larger collecting tubules and attains a diameter from 200–300 μ. The lining epithelium is composed of conspicuous clear simple columnar cells, about 20 μ in height and one-third as much in width, which rest upon a basement membrane. This type of epithelium extends almost as far as the end of the duct, and here becomes continuous with the stratified epithelium that covers the free surface of the papilla and lines the calyx.

The Supporting Tissue.—The uriniferous tubules and the blood-vessels are held in place by a delicate interstitial stroma of reticular connective tissue, elastic fibres being relatively very few. At the surface of the kidney this tissue is condensed into a compact fibrous stratum, the **tunica albuginea,** containing scattered bundles of unstriped muscle and an increasing number of elastic fibres, not to be confounded with the fibrous capsule that envelops the organ and may be stripped off without disturbing the renal substance. Although forming a continuous framework throughout the kidney, the interstitial stroma is not uniformly distributed, being most abundant along the path of the interlobar and the larger blood-vessels from whose adventitia delicate trabeculæ extend in all directions to form the meshes lodging the tubules, the smaller vessels and the capillaries. Within the cortex the supporting tissue is meagre, being best developed along the interlobular vessels and around the renal corpuscles. The interstitial tissue is much more plentiful within the medulla than the cortex, its amount increasing towards the apex of the papilla, where considerable tracts of stroma-tissue separate the papillary ducts. The fibrous component increases steadily with age, and its amount between the papillary ducts in the papilla is demonstrably greater in each succeeding decade of later life (Walsh). Not only the blood-vessels, but also the nerve-trunks are provided with sheaths of renal stroma.

The **blood-vessels** supplying the kidney, branches of the renal **artery,** enter the renal substance through the vascular foramina surrounding the papillæ on the wall of the sinus. As they pass along the sides of the papillæ, their positions correspond to the primary interlobar tracts of connective tissue of the fetal kidney. On reaching the level of the bases of the renal pyramids, each **interlobar artery** breaks up into twigs, some of which pursue an irregularly arched course across the bases of the pyramids, thereby producing in places the impression of "arcades" at the junction of the medulla and cortex. From these arcuate arteries or their divisions arise the terminal branches which supply the cortex. The cortical branches radiate generally perpendicular to the free surface, towards which, as the **interlobular arterioles,** they pass, giving off the short lateral twigs that end in the vasa afferentia of the glomeruli. Some of the terminals continue to the free surface where, in conjunction with direct **capsular branches** from the renal artery, they supply the capsule of the kidney. After traversing the capillary

complex of the glomerulus, the blood is carried off by the vas efferens, which on its exit immediately resolves into the **cortical capillaries,** whose meshes about the convoluted tubules are round and about the tubules of the medul-

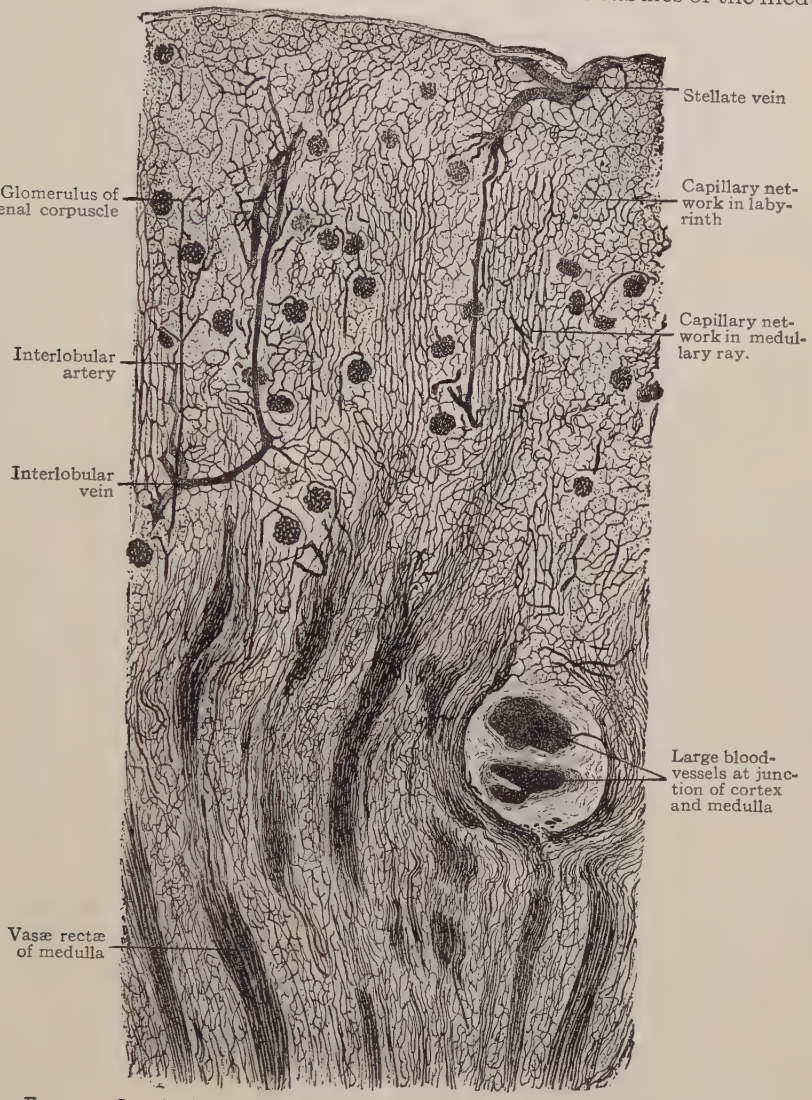


FIG. 273—Longitudinal section of injected kidney of a dog, showing general arrangement of blood-vessels, of cortex and adjoining medulla. × 40.

lary rays are elongated. In addition to the usual path through the glomerulus, the kidney-substance is supplied also by terminal vessels that pass directly into the intertubular network. The course of the medullary twigs is influenced by the radial disposition of the tubules between which they run; they are, therefore, relatively straight, and, hence, known as **arteriolæ rectæ.**

They arise only exceptionally from the arcuate arteries, and chiefly from the afferent branches of low lying, perhaps atrophic (Huber), glomeruli. The supply of the medulla is, therefore, less independent than formerly believed.

The **veins** of the kidney are also disposed as cortical and medullary branches which empty into large stems, the so-called **venæ arciformes,** that cross the bases of the pyramids and become tributary to the large intralobar trunks. The blood within the cortical capillaries escapes by three paths:—(1) through small veins that pass from the outer third of the cortex towards the capsule, beneath which they empty into stems running parallel to the free surface of the kidney; from three to five of these horizontal vessels converge to form a star-like channel, the **vena stellata,** which is the beginning of the **interlobular vein** that passes through the cortex with the corresponding arteriole to the arcuate veins at the base of the pyramid; (2) through small veins that empty directly into the interlobular veins at various levels; (3) through the deep cortical veins that traverse the inner third of the cortex and are direct tributaries of the venæ arciformes. The medulla is drained by the venulæ rectæ, straight vessels that begin in the medullary capillary network and empty for the most part indirectly in the arcuate veins. The latter terminate in the larger interlobular veins, which accompany the corresponding arteries along the sides of the pyramids and emerge into the sinus around the papillæ to become tributary to the renal vein. This vessel and its branches are without valves.

The **lymphatics** of the kidney occur as deeper and superficial networks. The **deep lymphatics** arise as networks of capillaries within the cortex and medulla, the general path of the more definite lymph-channels being that of the blood-vessels, from four to seven large trunks emerging at the hilum. The **superficial lymphatics** include two networks, one situated within or beneath the fibrous capsule and the other within the perirenal fatty areolar tissue (**capsula adiposa**). The subcapsular channels communicate with the peripheral parts of the cortical network, as well as with the vessels outside the fibrous capsule.

The **nerves** supplying the kidney are derived from the renal sympathetic plexus and consist, therefore, principally of unmyelinated fibres. These accompany the blood-vessels, around which they form plexuses containing ganglion-cells, and to which they send filaments for the walls. The smaller arteries are accompanied by the nerves as far as the glomeruli and capillaries. The relation between the nerve-fibres and the tubules is intimate, delicate filaments enclosing the convoluted canals with a network outside the basement membrane (epilemmar plexus), from which filaments pass to the inner side of the membrane (hypolemmar) and end partly between the epithelial cells.

THE RENAL DUCTS

Each canal consists of the greatly expanded upper end, the **renal pelvis** with its subdivisions, the **calyces,** and the main part of the duct, the **ureter,** the whole serving for the collection of the urine as it escapes from the kidney-tubes and for its transmission to the bladder.

The wall of all parts of the renal duct is the same in its general structure and consists of three layers: (1) the **mucous**, (2) the **muscular,** and (3) the **fibrous;** the mucous and muscular layers are more or less blended, so that a distinct submucosa is wanting. The **mucous membrane** is clothed with **transitional epithelium** consisting of several strata of cells, the deepest elements being irregularly columnar and the superficial ones to a varying degree flattened. The tunica propria is made up of bundles of fibrous tissue, intermingled with comparatively few elastic fibres, and is often directly attached to the muscular coat, a meagre amount of loose fibro-elastic tissue in places suggesting a submucous layer. Within the ureter, the mucous

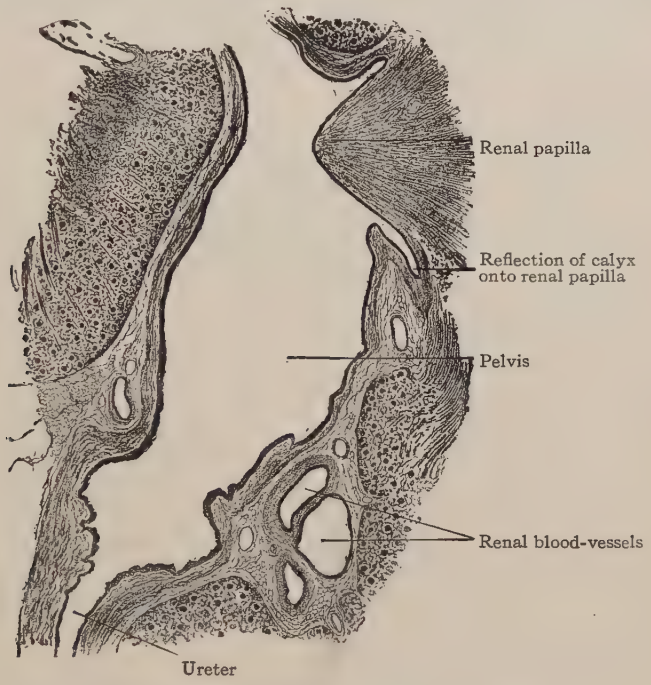


FIG. 274—Longitudinal section through sinus of child's kidney, showing lower part of pelvis and commencement of ureter. × 10.

membrane is usually thrown into longitudinal folds and, hence, the lumen appears stellate in transverse sections. Neither well-marked papillæ nor true glands are present. Numerous scattered free cells are ordinarily encountered within the tunica propria; sometimes, particularly in the vicinity of the calyces, there are distinct minute lymph-nodules. On the ends of the papillæ the epithelium is continuous with that of the papillary canals, and at the sides of the papillæ, the epithelium is reflected back as the lining of the calyces.

The **muscular tunic** consists of loosely connected bundles of unstriped tissue whose continuity as definite sheets is interrupted by often considerable intervening fibrous tissue. The muscle-bundles are arranged as a thin and imperfect **longitudinal** and a thicker and chief external **circular** layer.

Within the renal pelvis and its larger subdivisions, the infundibula, both layers are well represented, but are reduced on the calyces, except at the junction of the latter with the renal papillæ where the circular muscle is augmented and surrounds each papilla with a minute sphincter-like bundle. In the lower half of the ureter, an additional but incomplete external longitudinal layer is found outside the circular one. At its end, where the ureter meets and traverses very obliquely the wall of the bladder, the muscular tissue is represented almost exclusively by a well developed layer of longitudinal fibres, which retain their independence and do not blend with the vesical muscle but end in the mucosa of the bladder. Contraction of these fibres tends to dilate the ureteral orifices.

The **fibrous coat,** or **tunica adventitia,** composed of bundles of fibro-elastic tissue, invests the entire renal duct as its outermost tunic and con-

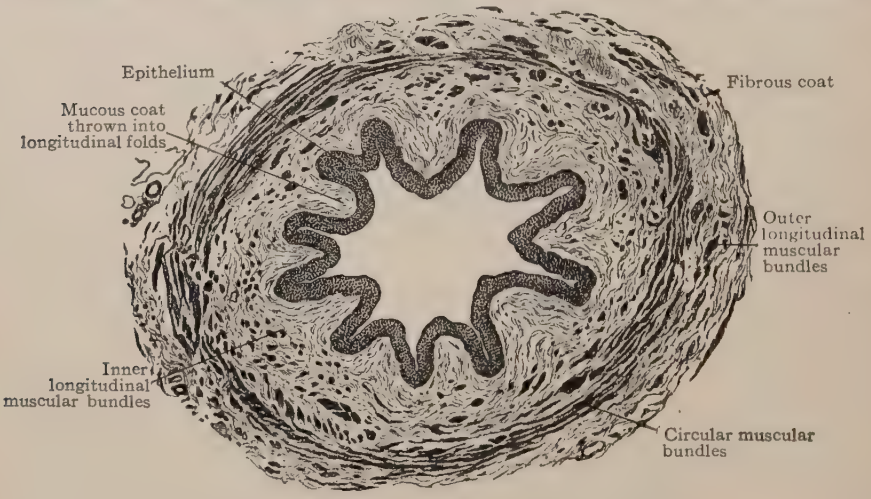


FIG. 275—Transverse section of ureter. × 25.

nects it, through the surrounding areolar tissue, with the adjacent structures. Within the sinus of the kidney, the outer coat of the renal duct blends with the tunica fibrosa that invests the renal substance where the latter is not embraced within the calyces. Just above the bladder the fibrous coat of the ureter becomes thicker and, in conjunction with the longitudinal muscle, forms the **ureteral sheath,** giving independence to the duct as it passes through the wall of the bladder.

The **blood-vessels** supplying the renal duct, derived from several sources during its long course through the abdomen and pelvis, break up into capillaries which are especially numerous within the tunica propria immediately beneath the epithelium. The veins begin within the mucosa, beneath which they form an inner plexus that communicates with a wider meshed outer plexus, lying within the fibrous coat and giving rise to the larger emergent venous trunks. The **lymphatics** within the mucous membrane are indefinite lymph-channels, but within the muscular coat and on

the surface are present as distinct networks from which afferent vessels pass to various groups of lymph-nodes. The **nerves** distributed to the renal duct are brought by branches from the neighboring sympathetic plexuses. While consisting chiefly of unmyelinated fibres destined for the muscular tissue and blood-vessels, many sensory fibres find their way into the mucous membrane, where some end within the tunica propria in free arborescent endings and others between the epithelial cells.

THE BLADDER

The bladder, the reservoir in which the urine is received from the renal ducts and retained until discharged through the urethra, is essentially a muscular sac, lined with mucous membrane and partly covered with peritoneum, a layer of connective tissue loosely uniting the mucous and muscular coats. From within outwards, four coats are distinguishable—the **mucous,** the **submucous,** the **muscular,** and the **fibrous.**

The **mucous coat** closely resembles that of the renal duct, consisting of a fibro-elastic tunica propria covered by **transitional epithelium.** The details of the latter are materially affected by the degree of contraction or distention to which the mucosa is subjected (Fig. 22). As ordinarily seen, the deepest cells are irregularly columnar, the ones of the middle layers polyhedral or club-shaped, and the large surface cells somewhat flattened with their deeper aspect modelled by the subjacent elements, over and between which fit depressions and projections. These surface cells are shed easily, and may be wanting on autopsy material. Although definite glands can hardly be said to exist, in the vicinity of the vesical trigone and of the urethral orifice the tunica propria contains small epithelial pockets, or crypts, from the bottom of which short branched tubules, lined with low columnar cells, extend into the surrounding stroma. These rudimentary glands have been interpreted as representing abortive prostatic tubules, which have become displaced during the development of the lower segment of the bladder from the uro-genital sinus.

The **submucous coat,** loose and elastic, permits free gliding of the mucous membrane over the muscular tunic when readjustment becomes necessary during contraction and the mucosa is strongly wrinkled. It is composed of bundles of fibrous tissue, interwoven with numerous elastic fibres, and supports the blood-vessels and nerve-plexuses and occasionally contains small lymph-nodules. The submucosa is not sharply defined from the adjacent coats, but blends with the tunica propria on the one side and penetrates between the tracts of muscle-bundles on the other. Beneath the trigonum a distinct submucous layer is wanting, or is replaced by a sheet of muscular tissue.

The **muscular coat,** thicker than the mucous and comparatively robust, varies according to the condition of the bladder, being thin during distention and very thick during strong contraction, when it may measure as much as 1.5 cm. The bundles of involuntary muscle are arranged as two fairly distinct chief layers—a thick circular and a thin outer longitudinal. Inside the circular, virtually within the mucosa, lies an incomplete

additional layer of mostly oblique bundles. The **longitudinal bundles,** best developed on the upper and lower surfaces of the bladder, do not form a continuous sheet, but interlace leaving intervals occupied by connective tissue. The **circular layer,** although more robust and uniform than the outer one, is weak and imperfect over the trigonal region and is well developed only above the level of the orifices of the ureters, towards the apex of the bladder becoming oblique and less regular. The innermost layer, largely represented by isolated and indefinite bundles intermingled with connective tissue, is condensed over the trigone, where it exists as a compact muscular sheet closely united with the overlying mucous membrane and surrounds the orifices of the ureters and of the urethra with sphincter-like bands.

The **fibrous coat,** composed of fibro-elastic bundles, is blended over

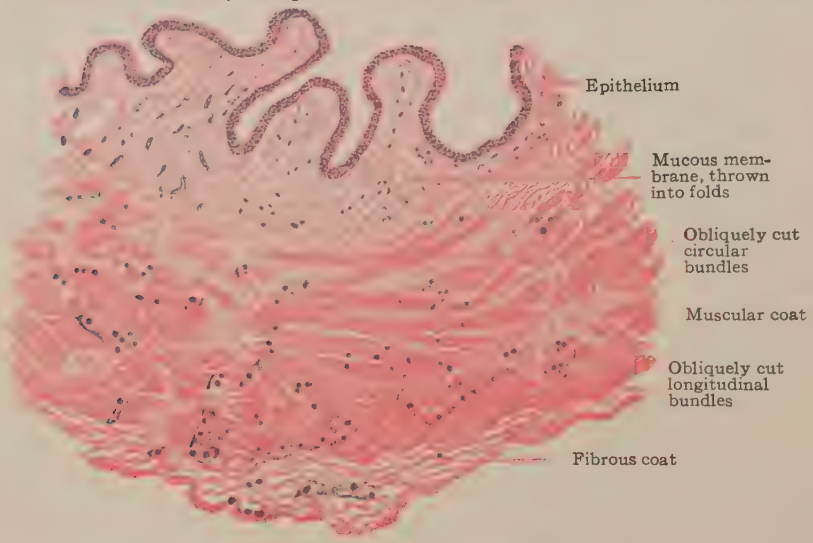


FIG. 276—Section of wall of bladder, showing general disposition of coats. × 12.

the upper and lateral surfaces of the bladder with the serous (peritoneal) covering; where this is wanting, it is continuous with the areolar tissue connecting the bladder with the surrounding pelvic wall and organs. It is strongest over the inferior surface, where it receives additions from the pelvic fascia, while towards the apex and beneath the peritoneum it is less definite and intermingled with adipose tissue.

The **blood-vessels** enclose the bladder with an arterial network within the fibrous coat, from which twigs enter the muscular coat and break up into capillaries, while others gain the submucous layer and form a network of the larger stems; from this branches pass into the mucous membrane and give rise to a rich capillary network immediately beneath the epithelium. The veins form a submucous plexus that drains the mucosa and empties into a muscular plexus, which, in turn, is tributary to the external subperitoneal plexus. With the exception of the smaller ones on the inferior surface, the vesical veins possess valves. The **lymphatics** begin as a close-meshed plexus

within the muscular coat, distinct lymph-channels being absent within the mucous membrane. Outside the muscular coat they form a loose plexus within the fibrous tissue (subperitoneal), the lymphatics from the apex and body of the bladder coursing downward and laterad and those from the fundus upward.

The **nerves** include both spinal and sympathetic fibres, myelinated and unmyelinated, and within the fibrous coat are connected with ganglia, particularly in the vicinity of the ureters, from which twigs enter the muscular coat and break up into smaller ones bearing microscopic ganglia. Other branches gain the submucous layer, where they form plexiform enlargements containing numerous groups of ganglion-cells; in addition to sympathetic filaments to the blood-vessels, fine bundles of fibres proceed to the mucous membrane to end in free terminations, partly within the tunica propria and, probably to some extent between the epithelial cells. The general sensibility of the normal bladder is comparatively slight, being greatest in the trigonal region, especially at the ureteral openings.

THE URETHRA

The urethra—the canal through which the urine is conveyed from the bladder to the exterior of the body—differs in the two sexes, since in the male, in addition to its common function of conducting the urine, it serves for the escape of the secretions of the sexual glands.

The Female Urethra.—The wall of this canal, much shorter (about

FIG. 277—Longitudinal section of wall of female urethra. × 50.

3.5 cm.) than the urethra in the male, consists essentially of a mucous membrane supplemented by a robust muscular tunic. The **mucous membrane,** thrown into longitudinal folds, is composed of a tunica propria, rich in elastic fibres, wandering cells and plexiform veins, and a layer of epithelium. The latter resembles that of the bladder above and that of the vestibule, into which the canal opens, below, but for the most part is stratified columnar epithelium. In the female the **urethral glands** are represented by small tubular alveoli that open by minute ducts on the mucous surface and

correspond to Littré's glands in the male. They are most plentiful in the upper part of the urethra and in aged subjects may contain concretions. The mucosa is also pitted with small crypts, similar to those in the male canal, into which the ducts of the glands often open.

The intrinsic **muscular tissue** of the female urethra is disposed as an inner layer of longitudinal and an outer one of circular involuntary fibres, the two being separated by a thin connective tissue stratum with many elastic fibres. At the internal urethral orifice, in conjunction with fibres from the trigonum of the bladder, the circular fibres aid in forming the internal vesical sphincter. The extrinsic muscular tissue is of the voluntary type. Thus, the lower end of the urethra is embraced by the anterior fibres of the sphincter vaginæ muscle, and higher, between the layers of the triangular ligament, the canal is surrounded by the bundles of the compressor urethræ. The deepest part of the mucosa and the adjacent portion of the longitudinal muscle layer in places contain such a rich venous plexus that the tissue resembles a cavernous structure.

The Male Urethra.—Considered with regard to the regions of the body in which it lies, the male urethra may be divided into a **pelvic,** a **perineal**, and a **penile** portion. It is more usual, however, to describe the canal as consisting of the **prostatic,** the **membranous,** and the **spongy** portions—a division based on the anatomical relations to the structures through which it passes.

The wall of the urethra consists of a **mucous membrane** containing a rich venous plexus and supplemented in the prostatic and membranous portions by considerable tracts of muscular tissue. The tunica propria possesses an unusual number of fine elastic fibres and is covered with an epithelium that varies in different parts of the canal. Throughout the upper two-thirds of the prostatic portion, the epithelium resembles that of the bladder, being of the transitional variety; on approaching the membranous portion, the epithelium becomes stratified columnar in type, the superficial elements being often goblet-cells. Except within the beginning of the spongy portion (pars cavernosa), where the lining is reduced to practically a single stratum of cells, the columnar epithelium retains its stratified character as far as the navicular fossa, the dilated distal end of the urethra. Here the epithelium becomes stratified squamous and at the external urethral orifice is directly continuous with the epidermis covering the glans penis. Within the urethral crest, the longitudinal ridge on the dorsal wall of the prostatic portion of the canal, the mucous membrane acquires the character of erectile tissue on account of the abundance of the venous channels occupying the deeper layer of the tunica propria.

The **muscular tissue** associated with the male urethra includes intrinsic and extrinsic fibres, the former being involuntary and directly incorporated with the wall of the canal and the latter being accessory strands of striped muscle derived from structures surrounding the urethra. The intrinsic muscle is arranged as an inner longitudinal and an outer circular layer, of which the longitudinal is thinner, but more widely distributed extending from the internal urethral orifice at the bladder as far

forwards as the openings of the bulbo-urethral glands in the pars cavernosa. The circular fibres, outside the longitudinal ones, are best developed at the internal urethral orifice where they are three or four times as thick as those running lengthwise. They gradually diminish and just beyond the membranous urethra disappear, first on the lower and last on the upper wall of the dilatation, the fossa bulbi. In advance of the posterior third of the spongy portion, the intrinsic muscle is wanting, the unstriped muscular tissue surrounding the remainder of the canal belonging to the erectile tissue of the corpus spongiosum which the urethra traverses. The **internal vesical sphincter**, encircling the commencement of the urethra is composed of the circular fibres of involuntary muscle mentioned above, reinforced by fibres derived from the muscular sheet of the trigonum of the bladder. At the apex of the prostate gland, the urethra is surrounded by bundles of striped

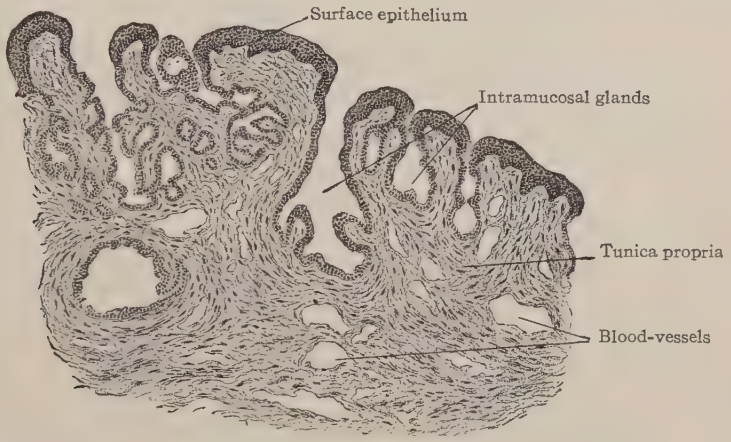


FIG. 278—Section of mucous membrane of prostatic urethra, showing gland-like crypts in mucosa. × 45.

muscle, known as the **external vesical sphincter,** prolonged upwards from the compressor urethræ muscle.

The **urethral glands,** or **glands of Littré,** embrace two groups, those within the mucous membrane and those immediately outside, whose ducts are seen with a magnifying glass as minute openings on the mucous surface. The former, the **intramucosal glands,** are small and simple, consisting usually of a single alveolus, less frequently of two or three. They are lined with columnar epithelium and occur in all parts of the urethra, but are most numerous in the spongy portion. The **extramucosal glands,** although small, are larger than the preceding, but less widely distributed, since they are absent in the distal half of the membranous and in the proximal third of the spongy portion. Their ducts often extend several millimeters obliquely backwards, more or less parallel to the urethra, and divide into several slightly expanded alveoli, lined with columnar epithelium. In addition to the foregoing true, although small glands, the urethral mucosa is beset, along its upper wall, with small diverticula, the **lacunæ urethrales,** which are little

more than tubular depressions, or **crypts,** within the mucous membrane and can not be regarded as glands, although they often receive the ducts of the extramucosal glandules. One crypt of exceptional size (4–12 mm. in depth) is commonly found on the roof of the navicular fossa, its orifice being guarded by a fold of mucous membrane.

The **blood-vessels** supplying the urethra provide a generous capillary network beneath the epithelium; it is, however, the unusual abundance of the venous channels that confers the exceptional cavernous character of the wall of the canal. The **lymphatics** are also numerous within the deeper parts of the mucosa in the male, especially in the region of the glans penis;

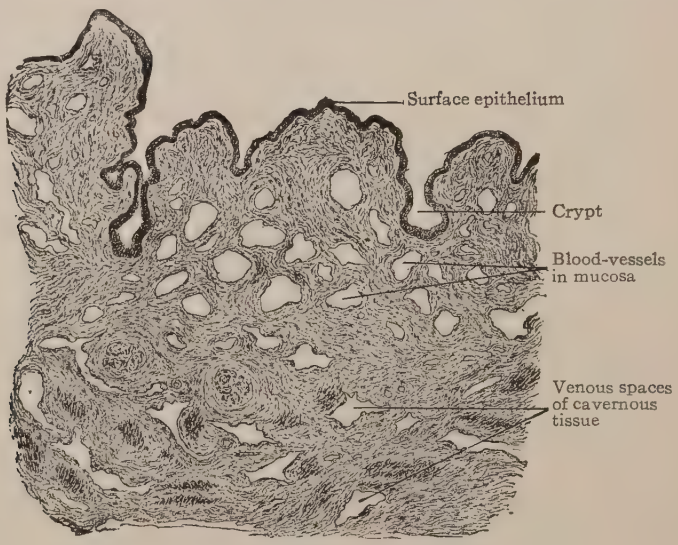


FIG. 279—Section of wall of urethra, spongy portion, showing crypts and blood-spaces in mucosa. × 35.

towards the upper end of the urethra they diminish, those from the prostatic portion communicating with the intramuscular network at the neck of the bladder. The lymphatics of the female urethra correspond with those of the membranous and prostatic portions of the male duct. The **nerves** include branches from the pudic (sensory fibres to the mucous membrane and motor fibres to the associated striped muscle) and from the hypogastric plexus of the sympathetic by way of the prostatic and cavernous plexus. The plexiform sympathetic fibres, associated with numerous ganglion-cells along their course supply the involuntary muscle and the walls of the blood-vessels. The sensory fibres are distributed to the mucous membrane in which they end mostly as free, but to some extent as special terminations within the tunica propria, although some filaments penetrate between the epithelial cells.

THE MALE REPRODUCTIVE ORGANS

THESE include: the sexual glands (the **testes**), the spermatic ducts (**epididymes** and **vasa deferentia**) and their appendages (the **seminal vesicles**), the copulative organ (the **penis**), and certain accessory glands (the **prostate** and the **bulbo-urethral glands**). At first situated within the abdomen the testes migrate during the last few weeks of fetal life through the inguinal canal into the scrotum, gaining the latter usually shortly before birth. In their descent they are accompanied by blood-vessels, lymphatics, nerves, and their ducts, which structures, with the supporting and investing tissue, constitute the **spermatic cord** that extends through the abdominal wall to the scrotum.

THE TESTIS

As often employed the term "testicle" includes two essentially different parts, the **testis,** the organ producing the male sex-cells (sperms or spermatozoa) and the **epididymis,** the highly convoluted commencement of the spermatic duct. The testes, or testicles proper, are two ellipsoidal bodies obliquely suspended within the scrotum. Each testis measures about 4 cm. in length, 2.5 cm. in breadth and 2 cm. in thickness. With the exception of the posterior border where the vessels, nerves, and ducts enter and emerge, the testis is covered with a serous membrane, the **tunica vaginalis.**

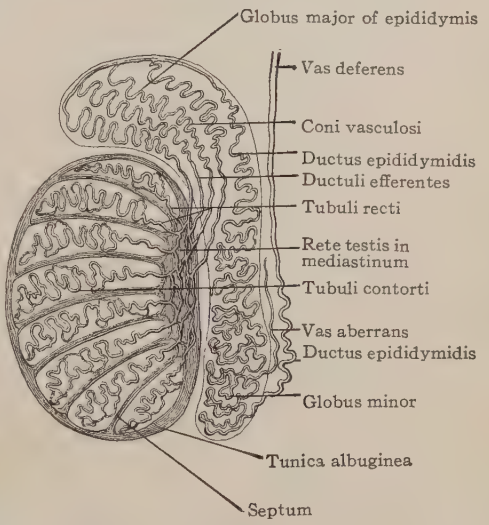


FIG. 280—Diagram illustrating architecture of the testicle.

Architecture of the Testicle.—The **framework** of the testicle proper includes a stout fibro-elastic capsule, the **tunica albuginea,** .4–.6 mm. in thickness, that gives form to the organ and protects the enclosed softer tissues. Along the posterior border of the testis the capsule is greatly thickened, forming the **mediastinum testis,** from which radiate a number of membranous **septa** that pass to the inner surface of the tunica albuginea. In this way the space enclosed by the capsule is subdivided into pyramidal compartments (Fig. 280), the bases of which lie at the periphery and the apices at the mediastinum. These spaces contain collectively from 150 to 200 pyriform masses of spermiogenetic tissue, more or less separated from one another, which are the **lobules.** Each of the latter is made up of

from one to three greatly convoluted **seminiferous tubules,** held together by delicate connective tissue. These tubules, from 25–70 cm. long, are, at least in the rabbit, arched, not blind, canals connected by both ends with a tubulus rectus. They are very tortuous (**tubuli contorti**) until they con-

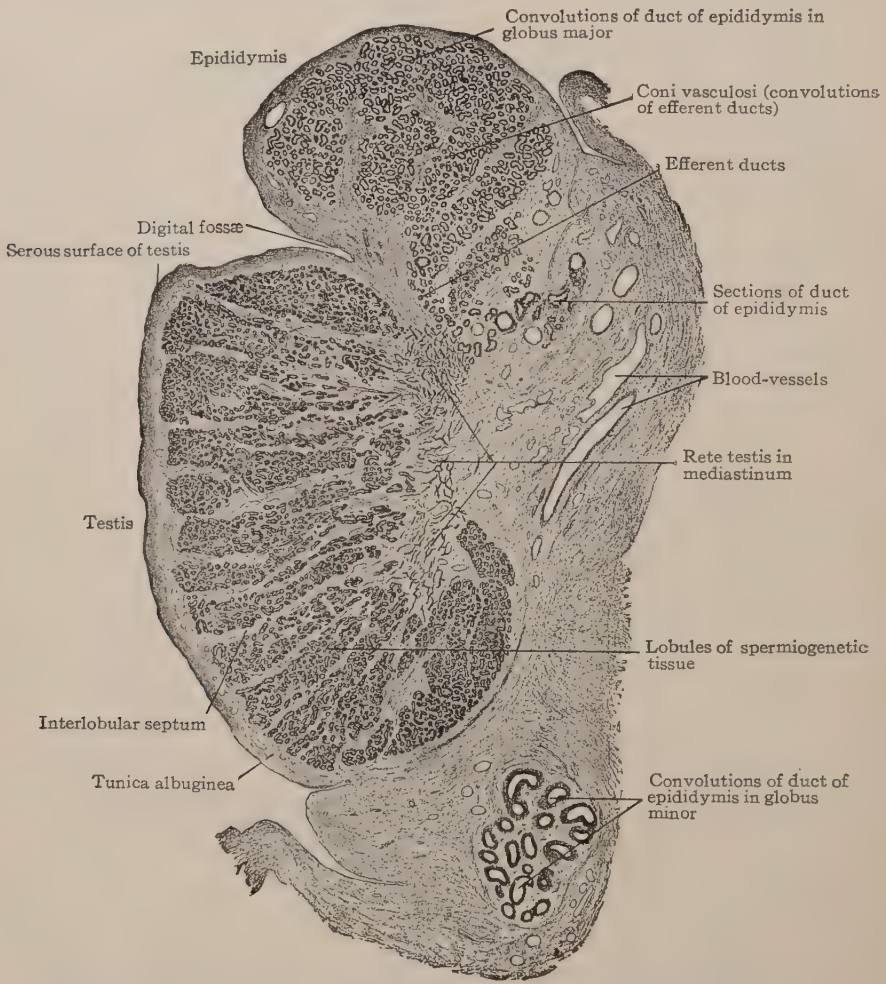


FIG. 281—Longitudinal section of testicle of child, showing arrangement of framework and gland-tissue and of canals connecting testis with epididymis. × 10.

verge at the apex of the lobule. Here they pass, after occasional union with another canal, into the straight tubules (**tubuli recti**) that enter the mediastinum and join to form a close network, the **rete testis.** The latter extends almost the entire length of the mediastinum and consists of a system of irregular intercommunicating channels lined with cuboidal epithelium. With these passages the canals of the testicle proper end, the immediate

continuation of the spermatic path being from 15–20 tubules, the **ductuli efferentes,** that pierce the tunica albuginea along the posterior border of the testis near the upper pole and, forming the tortuous **coni vasculosi,**

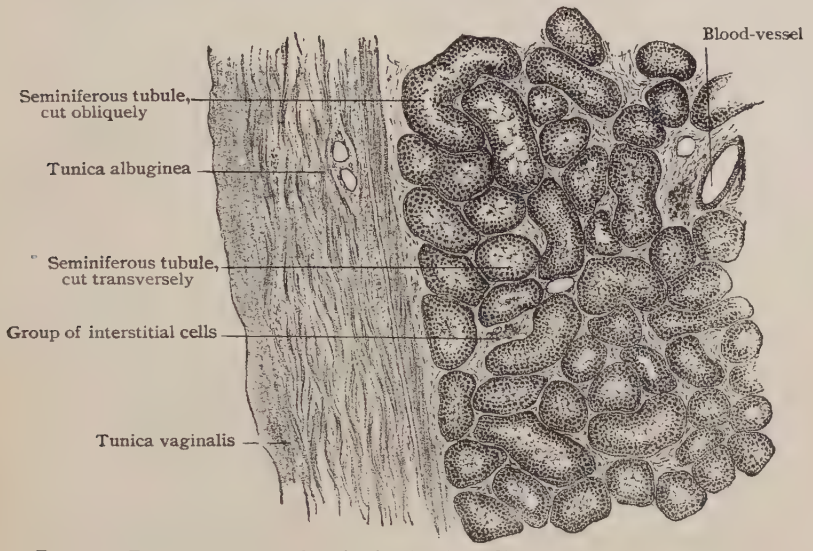


FIG. 282—Transverse section of testis, showing dense fibrous capsule and adjacent seminiferous tubules. × 30.

connect the sexual gland with the beginning of the spermatic duct, the highly convoluted **ductus epididymidis.**

In contrast to the dense fibro-elastic tissue of the framework of the testis, the **interstitial connective tissue** between the seminiferous tubules is loose, consisting of delicate bundles of white fibrous tissue with few elastic fibres. In addition to fixed and wandering connective tissue cells that occur in varying numbers, the intertubular, or interstitial, stroma contains groups or cord-like masses of peculiar rounded polygonal elements, the **interstitial cells.** These cells (15–20 μ in diameter) possess relatively small eccentric nuclei and finely granular cytoplasm that usually lodges numerous fatty droplets, pigment granules, crystalloids, and mitochondria in the form of minute granules and rods. The significance of these

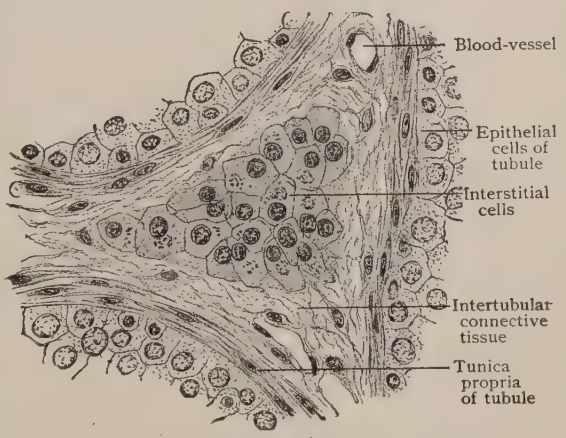


FIG. 283—Group of interstitial cells lying within intertubular stroma.

cells is uncertain, but they are probably modified connective tissue elements concerned in the production of an internal secretion.

The Seminiferous Tubules.—These consist of a tunica propria, or basement membrane, which encloses several layers of epithelial cells. Their histological appearance is different before and after puberty and varies subsequent to the latter with functional activity or rest. As seen in sections of the mature human testicle (Fig. 284), the epithelial lining of the seminiferous tubules includes two chief varieties of cells, the **supporting** and the **spermiogenetic.** The former, the **Sertoli cells,** take no active part

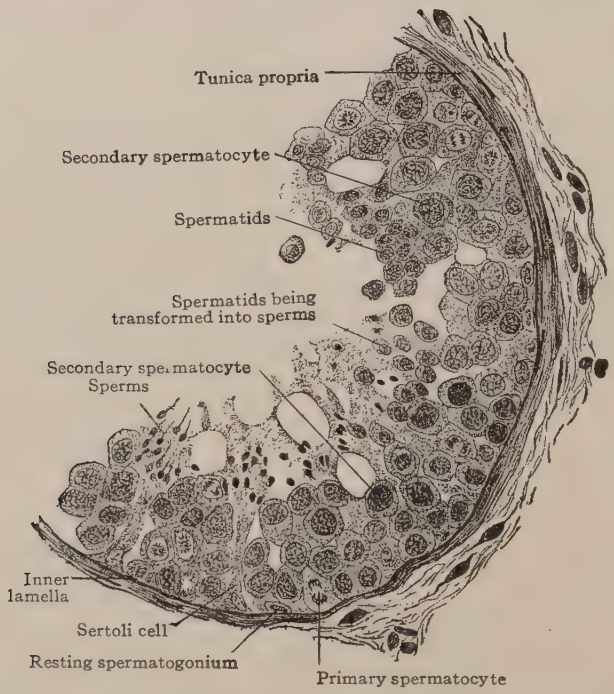


FIG. 284.—Portion of a seminiferous tubule, cut transversely, showing the lining cells in various stages of spermiogenesis. ×350.

in the production of the sperms, but serve as temporary supports and purveyors of nutrition for the more essential elements during the final stages of spermiogenesis. They are elongated irregularly pyramidal in form and rest upon the membrana propria by expanded bases which are in continuity with one another. Their large oval nuclei are meagre in chromatin and hence palely-staining, and lie within the basal expansions. Their apices project between the surrounding spermiogenetic cells toward the lumen of the tube. The outer part of the cytoplasm contains fat-droplets, the inner zone being granular or longitudinally striated. Often their apical portions may be identified by the grouping of the heads of the developing sperms about them. Where the convoluted tubules pass into the straight ones, the Sertoli cells become reduced in height, and form a layer of simple columnar

cells continuous with the low cuboidal epithelium that lines the rete testis in the mediastinum.

The **spermiogenetic cells** are concerned in the cytological cycle, known as **spermiogenesis** or **spermatogenesis,** whereby the sperms are produced from the cells lining the seminiferous tubules. They include four forms that stand in the relation of succeeding generations to one another, those representing the first, or oldest, lying nearest the membrana propria and the last, or youngest, from which the mature sex-cells are directly derived, next the lumen of the tubule.

FIG. 285—Diagram illustrating phases of one complete cycle of spermiogenesis in rat. Sequence of figures show in detail growth (1-6) and division (7-8) of spermatogone; growth and division of primary spermatocyte (9-19) into secondary spermatocytes; division of latter (20-21) into spermatids (22-24); spermioblasts (25-26); differentiation (27-31) and final liberation (32) of sperms. (*After Ebner.*)

The first generation, the **spermatogonia,** lie at the periphery between the Sertoli cells and, although small round elements, possess nuclei exceedingly rich in chromatin. The division of the spermatogonium results in two cells, of which one retains the position of the parent cell (which it replaces as a new spermatogonium destined for a succeeding division), while the other passes inwards, enlarges and becomes a **primary spermatocyte.** This element, conspicuous by reason of its size and large nucleus, undergoes mitotic division and gives rise to two daughter cells, the **secondary spermatocytes,** or **prespermatids.** The latter almost immediately divide and produce smaller cells, the **spermatids,** by whose transformation the sperms directly arise. It is important to note that the spermatids contain only one-half of the number of chromosomes normal for the ordinary (somatic) cells of the human body, a like reduction occurring during the maturation of the ovum. The spermatids, at first small cells with round nuclei, elongate; their nuclei coincidently become oval and smaller, but rich in chromatin, and shift to the end of the cell most removed from the lumen of the tubule. The modified spermatids now become grouped in close relation to the Sertoli cells, and are called **spermioblasts.** The succeeding changes include the transformation of the elongated nucleus of the spermioblast into the

head, and of its double centrosome (diplosome) into the neck-granules and (according to some), the axial filament of the sperm, while from the cytoplasm of the spermatid its remaining parts are derived. As the sperms become more and more differentiated, they appear as fan-shaped groups in which the heads are always buried within the ends of the Sertoli cells and the tails directed towards the lumen of the canal. After subsequent separation, the liberated spermatic filaments occupy the centre of the tubule as masses which often fill the lumen and in which the sperms are disposed in peculiar whorl-like groups. Their completed development, however, is deferred until they reach the canal of the epididymis, during the passage of which long and highly tortuous path they attain maturity. Production of sperms which occurs only within the convoluted seminiferous tubules does not involve uniformly all parts of the tubule, but proceeds with wave-like periodicity; consequently, cross-sections of the same tubule taken a few millimeters apart exhibit different stages of the spermatogenetic cycle.

FIG. 286—Human spermatozoa; one head is seen in profile. × 560.

The **spermia, spermatozoa** or **spermatic filaments,** the essential male reproductive elements are, like the ova, direct descendants of primary germ cells. Unlike the ova, however, which are rounded, relatively large and often absolutely huge cells, the sperms are small filaments and present great diversity in size, form, and detail and exhibit a high degree of specialization. As ordinarily seen under moderately high magnification (Fig. 286), three parts may be recognized—the **head,** the **neck,** and the **tail.** The head is ovoid, flattened in front so that when viewed in profile it appears pyriform. Although rich in chromatin, the latter is not arranged as threads or networks, but is condensed so that the head appears homogeneous. Of the 50–60 μ representing the approximate entire length of the human sperm, the head contributes about one-tenth (5–6 μ). The **neck,** uniting the head and the tail, is in man slightly constricted and, therefore, not easily seen, its position being indicated by the ready separation of the head from the tail at this point. It contains the minute anterior and posterior centrosomes, or **neck-granules.** The **tail** is regarded as composed of three segments: the **connecting piece** (6 μ), the **chief piece** (40 μ), and the **end piece** (10 μ). The tail is traversed throughout its length by an extremely delicate **axial fibril,** which (except in the end piece, where the axial fibril is naked) is invested by an attenuated protoplasmic sheath. In the connecting

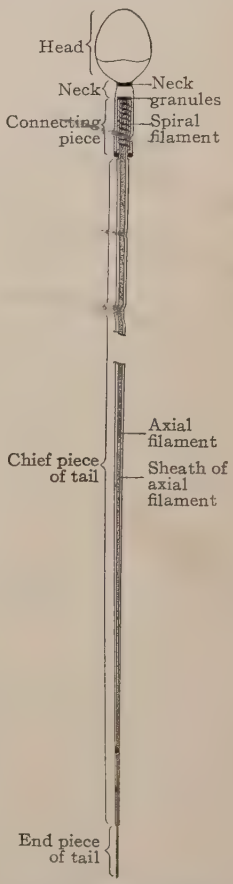


FIG. 287—Diagram illustrating structural details of human spermatozoon. (*Meves.*)

piece (middle piece) the axial fibre is supposed to be surrounded by a spiral fibre, the posterior limit corresponding with a minute **end-disk.** Beyond the recognition of the chief parts of the sperm—the head, neck, and tail—little can be seen of the above noted details unless the observer be provided with specially stained preparations and lenses of the highest power and most perfect definition. The living sperms as seen in fresh semen, display active movements, rapidly changing their position in consequence of the vibrations of the long motile flagellum, the tail. The actual rate of their unobstructed progress has been estimated at from 1.5–3.5 mm. per minute. Although less vigorous than in the semen the sperms often display motion in the secretion as taken from the epididymis. Sperms may continue to exhibit motion for a long time, in the body for several days after death; in properly guarded microscopical preparations of fresh semen movements have been observed after the lapse of over eight days. They may remain active probably for even a longer period within the female generative tract. Although resisting a wide range of temperature, sperms immediately succumb to aqueous solutions containing acids or metallic salts; alkaline solutions, on the other hand, stimulate their motion. Ejaculated **semen** is a composite fluid, consisting of the secretions of the testicle diluted with those from the seminal vesicles, the prostate and the bulbo-urethral glands. It has been estimated that each cubic millimeter of semen contains approximately 60,000 sperms.

THE EPIDIDYMIS

The epididymis, the greatly convoluted beginning of the spermatic duct, is a crescentic body that covers the posterior border and part of the outer surface of the testis. Its enlarged upper end, or head, the **globus major,** is succeeded by the tapering **body,** at the lower end of which is a second but smaller enlargement, the **globus minor.** The bulk of the globus major depends upon the aggregation of from twelve to fifteen conical masses, the **lobuli epididymidis,** formed by the **efferent ducts** and their tortuosities, the **coni vasculosi,** that pass from the upper end of the testis and connect the rete testis with the **canal of the epididymis.** The latter, also called the **ductus epididymidis,** begins in the globus major, receives the efferent ducts and becomes greatly convoluted, the remarkably wound single tube measuring when unravelled, from 5–5.5 meters or from 18–20 feet.

The **efferent ducts** form the conical lobules of the globus major, which masses, together with the convolutions of the canal of the epididymis, are enclosed by a fibrous envelope resembling but less robust than the capsule of the testis. The individual tubules and convolutions are held together by delicate vascular connective tissue. The transition of the irregular channels of the rete testis into the efferent ducts (.2–.5 mm. in diameter) is marked by an abrupt change in the character of the lining epithelium, the low cuboidal cells of the former giving place to irregularly ciliated columnar ones within the efferent ducts. This epithelium, moreover, is composed of cells of unequal height, some forming groups of tall cylindrical elements, with or without cilia and variably pigmented, while others occur as groups of low

cuboidal cells. In consequence of this inequality, the lumen of the efferent ducts is irregular and the surface of the mucous membrane modelled with minute depressions corresponding to the areas covered by the lower cells. In some cells the border of cilia is replaced by clear caps, which have been interpreted as secretion. Outside a well defined basement membrane the tubules are surrounded with a layer of circularly disposed unstriped muscle, intermingled with numerous elastic fibres.

The **canal of the epididymis,** from .4–.5 mm. in diameter, is lined throughout with stratified ciliated columnar epithelium, consisting of a deep layer of small rounded cells, next the well defined basement membrane, and a superficial layer of tall columnar elements, that contain pigment particles and secretion granules. The free surfaces of the columnar cells bear exceptionally long cilia, which, however, are not motile. In places the epithelium contains minute tubular diverticula that are regarded as abortive glands. Outside the membrana propria the duct is enclosed by a robust circular layer of unstriped muscle (15–30 μ thick), which attains its greatest development within the globus minor, near the beginning of the vas deferens. The convolutions of the canal are held together and in place by intervening fibro-elastic tissue.

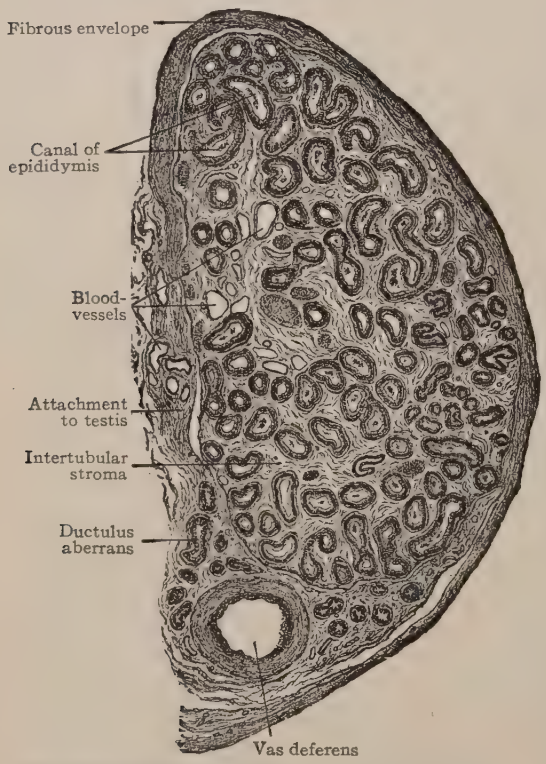


FIG. 288—Section across lower part of epididymis. × 15.

The **blood-vessels** supplying the testicle are branches from the spermatic and deferential arteries, those from the former being distributed especially to the testis and those from the latter to the epididymis. The spermatic branches enter the mediastinum and break up into superficial and deep twigs that follow the tunica albuginea and the septa, respectively. They continue within the tracts of intertubular connective tissue and ultimately form rich capillary networks enclosing the seminiferous tubule immediately outside the basement membrane. The arteries distributed to the epididymis course within the intertubular stroma and likewise resolve into capillaries that enclose the efferent ducts and the convolutions of the

canal of the epididymis. The **veins** arise from the capillary networks; those from the testis, superficial and deep, emerge at the mediastinum and, joining with those from the globus major, concentrate into several stems of considerable size that ascend within the spermatic cord in the anterior part of the pampiniform plexus. The veins from the body and tail of the epididymis unite into a smaller group that ascends in the posterior part of the plexus.

The **lymphatics** of the testis begin in the connective tissue surrounding the tubules and follow, in a general way, the course of the veins as a superficial and a deep set. They emerge from the mediastinum as six to eight relatively large trunks, to which the lymphatics of the epididymis are tributary, and accompany the veins in the cord.

The **nerves** of the testicle are chiefly sympathetic fibres destined for the walls of the blood-vessels and the unstriped muscular tissue of the epididymis. They form plexuses enclosing microscopic ganglia around the larger vessels. The relation between the terminal fibres and the tubules includes epilemmar fibrils on the exterior of the basement membrane, and, perhaps, a few hypolemmar ones that penetrate between the epithelial cells.

VESTIGIAL APPENDAGES

Under this heading are included several vestigial organs that remain for a variable period, some throughout life, as more or less conspicuous bodies attached to the testis or the epididymis. They claim attention not only on account of their morphological relations, but also because they may become the seat of pathological changes. The most important are: the **appendix testis,** the **appendix epididymidis,** the **paradidymis,** and the **ductuli aberrantes.**

The **appendix testis,** also called the **unstalked or sessile hydatid,** is a small but fairly constant body, 5–10 mm. in length and less than half as broad, fixed to the upper pole of the testis. It consists of a vascular connective tissue stroma in which lies a minute canal of variable size and extent, lined with columnar epithelium. The appendage represents the atrophic upper end of the Müllerian duct, one of a pair of fetal tubes that in the female embryo give rise to the oviducts, the uterus, and the vagina.

The **appendix epididymidis,** or **stalked hydatid,** is a small pyriform sac, from 3–4 mm. in length, containing a clear fluid and lined with cuboidal epithelium. It is variable in form, size, and number, two or more sometimes being present, and is probably derived from the tubules of the fetal Wolffian body.

The **paradidymis,** or **organ of Giraldès,** consists of an irregular group of blind tubules, from 5–6 mm. in length, that lies within the lower end of the spermatic cord, above but close to the head of the epididymis. The tubules are lined with cuboidal or columnar ciliated epithelium and are derivatives of the Wolffian tubules.

The **ductuli aberrantes** include tubular appendages, usually an upper and a lower, that extend for an uncertain distance within the epididymis among the convolutions of its duct. The tubules are lined with ciliated columnar or cuboidal epithelial cells and are regarded as originating from the atrophic tubules of the Woffian body.

THE SPERMATIC DUCTS

The spermatic duct, in the more usual and restricted sense, is one of a pair of tortuous canals that connect the epididymis with the urethra and thus provide channels for the escape of the secretion of the sexual glands. Each duct is conventionally described as composed of the **vas deferens** with its **ampulla** and the **ejaculatory duct;** at the upper end of the latter the spermatic duct is connected with the **seminal vesicle,** a saccular organ derived as an outgrowth from the main canal.

The Vas Deferens.—This tube extends from the epididymis to the ejaculatory duct and, when straightened out, measures some 45 cm. (18 in.) thus contributing almost the entire length of the spermatic duct. Its diameter is from 2–3 mm. Within the spermatic cord (pars funicularis) the vas occupies a position behind the other constituents of the cord and may be recognized by the hard cord-like consistency imparted by its thick fibro-muscular wall. The latter (1–1.5 mm. thick) encloses a narrow lumen and consists of three coats—the mucous, muscular, and fibrous. The **mucous coat** is clothed with epithelium which for a considerable distance resembles that of the canal of the epididymis, being made up of a superficial layer of ciliated columnar and a deep one of small rounded cells. Throughout the upper part of the duct, however, the cells are lower, without cilia, and approach a

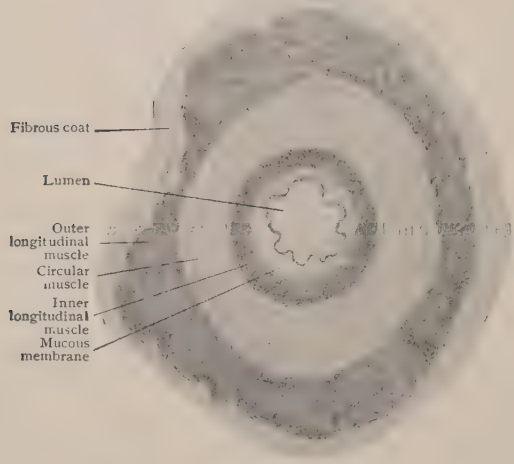


FIG. 289—Cross-section of vas deferens. × 15.

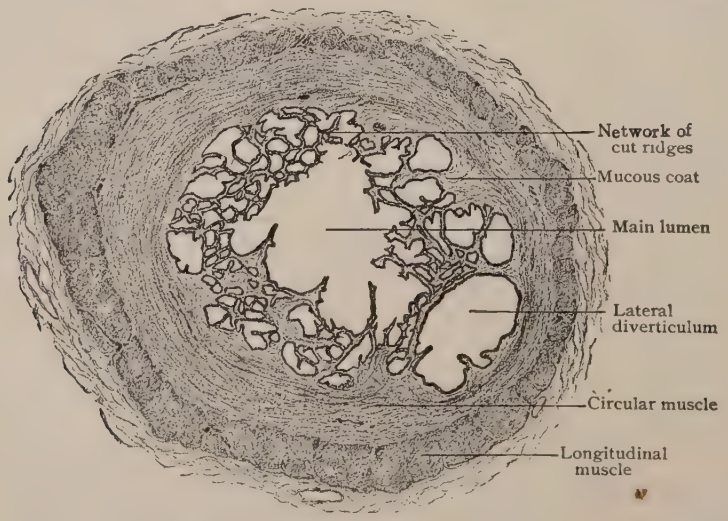


FIG. 290.—Transverse section of ampulla of spermatic duct (vas deferens). × 18.

simple cuboidal type. These cells show evidences of glandular activity and particles of pigment are common in their cytoplasm. The tunica propria contains a dense network of elastic fibres within its outer zone. The unusu-

ally robust **musculature** of the vas, from .8–1.2 mm. thick, constitutes approximately four-fifths of the entire wall and includes unstriped fibre arranged as an outer longitudinal, a middle circular, and an inner longitudinal layer, the last mentioned layer being much less developed than the outer and middle strata. The **fibrous coat** is composed of closely arranged bundles of fibrous tissue and many elastic fibres. In the funicular part of the duct, between the epididymis and the abdominal wall, the fibrous coat contains strands of unstriped muscle, which belong to the coverings of the cord and constitute the so-called internal cremaster.

The **ampulla,** the somewhat flattened fusiform enlargement of the vas just before it becomes the ejaculatory duct, is uneven and nodular in contour owing to the sacculations and tortuosity of the canal and the short diverticula that pass from the main duct at various angles. In its general structure the ampulla corresponds with the vas deferens, its walls, however, possessing a much thinner and less regular muscular coat—the inner longitudinal layer disappearing, the outer one being imperfect, and the orderly disposition of the circular fibres being disturbed by oblique bundles. The mucous membrane is modelled by numerous ridges and depressions and covered with a single layer of low columnar nonciliated epithelial cells.

The Ejaculatory Duct.—This, the terminal segment of the spermatic canal, although apparently formed by the union of the duct of the seminal vesicle and the vas deferens, is the morphological continuation of the vas, from which, when still represented by the embryonic Wolffian duct, the seminal vesicle develops as an outgrowth. The ejaculatory duct penetrates part of the prostate gland and ends in the urethra by a minute opening situated on the urethral crest, at the side of the orifice of the prostatic utricle. It possesses a structure essentially the same as that of other parts of the spermatic canal, its walls, however, being thinner than in the ampulla in consequence of the diminished thickness and incompleteness of the muscle. On reaching the ejaculatory duct the longitudinal muscle disappears and even the remaining circular bundles become greatly reduced and intermingled with fibrous tissue which almost replaces them. The surface of the duct, particularly along its upper wall, is broken by minute depressions and diverticula which recall, in miniature, those modelling the seminal vesicles. Some of these are branched tubules and recall tubo-alveolar glands. The character of the epithelium is inconstant, in places the lining being a single and in others a double layer of low columnar cells; within a short distance of the end of the duct, the epithelium assumes the transitional type found in the prostatic urethra.

The Seminal Vesicle.—This organ, one of a pair of sacculated appendages of the spermatic ducts, lies behind the bladder and in front of the rectum. Its general form is pear-shaped, with the base directed upwards and outwards and the abruptly tapering lower end converging to join the spermatic duct. When divested of the fibro-muscular capsule that blends the divisions into a knobbed mass, the organ may be separated into a **chief duct** and **diverticula,** all of which, after repeated windings, end blindly. The lumen of the chief duct, as seen in section (Fig. 292), is irregular,

constrictions and dilatations following one another with little order. The seminal vesicle contains a light brownish fluid in which sperms are usually found during the period of sexual activity.

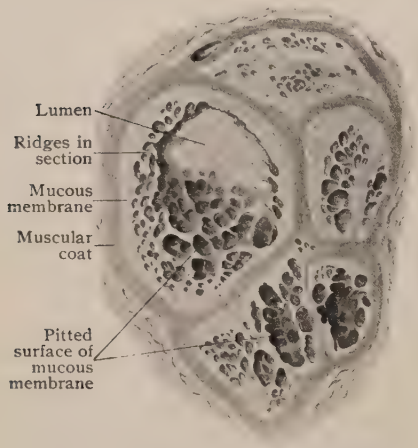


FIG. 291.—Cross-section of seminal vesicle, showing modelling of mucous surface. × 12.

In its general structure, the seminal vesicle resembles closely the ampulla of the vas deferens, possessing a robust muscular coat composed of an inner circular and an outer longitudinal layer of unstriped tissue. The mucous membrane is conspicuously modelled by numerous ridges and pits so that in sections it appears honeycombed (Fig. 291). The surface of the larger ridges is covered by two or three layers, that of the pits and diverticula by a single layer, of low columnar epithelial cells, many of which contain secretion-particles. Minute branched tubular canals, lined with low columnar epithelium containing goblet-cells and other evidences of secretory activity, extend into the mucosa from the bottom of the deeper recesses. Pigment granules are also constant after the advent of sexual maturity. The tunica propria is rich in elastic fibres. The fluid pro-

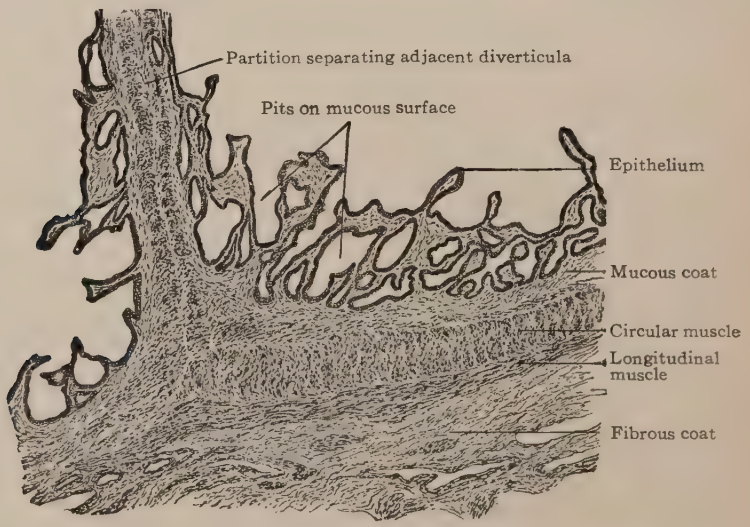


FIG. 292—Wall of seminal vesicle in longitudinal section, showing pitting of mucous coat. × 45.

duced within the seminal vesicles is of importance probably not only in diluting the secretion of the testicle and supplying a medium favorable for the motility of the sperms, but also in completing the volume of fluid

favorable for ejaculation (Waldeyer). The spermatic ducts, and not the vesicles, serve as the chief reservoirs for the sperms.

The **blood-vessels** supplying the spermatic duct and the seminal vesicle give off twigs that enter the walls and break up into capillary networks within the muscular and mucous coats. That within the latter occupies the superficial part of the tunica propria, immediately beneath the basement membrane. The **veins** begin within the deeper part of the mucosa and, after piercing the walls of the duct, and vesicle, unite into a superficial network, following the vas as the deferential plexus and surrounding the vesicle as the seminal plexus. Within the spermatic cord the former communicates with the pampiniform plexus, the component veins of which are distinguished by unusually well marked muscle.

The **lymphatics** of the seminal duct and vesicle are numerous and arranged as a deeper and a superficial set. The former arise from lymph-channels within the mucous and muscular coats and join the superficial network, outside the dense walls, from which efferent trunks pass to the lymph-nodes.

The **nerves** of the duct and vesicle are derived chiefly from the hypogastric sympathetic plexus; they surround the blood-vessels with plexiform meshes from which fibres pass into the muscular tissue where they form the dense **plexus myospermaticus**. The latter sends fibres to supply the unstriped muscle, while others penetrate the mucous membrane, and end mostly within the tunica propria, some fibrils gaining, perhaps, an intra-epithelial position.

THE PENIS

The male copulative organ consists of three cylinders of erectile tissue—the paired **corpora cavernosa** and single **corpus spongiosum**—united with one another and invested by coverings of fascia and skin. The anterior, or upper, and flattened surface of the penis is formed by the corpora cavernosa; the posterior or under surface corresponds to the corpus spongiosum, which is traversed by the urethra. The conical **glans penis,** forming the free end of the organ, is continuous with the corpus spongiosum which it resembles in structure.

Each of the cylinders of erectile tissue is enclosed by a robust sheath, the **tunica albuginea,** composed of dense fibrous tissue, intermingled with fine elastic fibres but no muscle. The sheath surrounding the corpora cavernosa, which includes an outer longitudinal and an inner circular layer and in places attains a thickness of over 1 mm. is much stronger than that enclosing the spongy body; it is, however, imperfect along the opposed median surfaces of the two cylinders, where it forms the **pectiniform septum.** From the inner surface of the tunica albuginea, fibrous septa and trabeculæ are given off which constitute the framework supporting the vessels and nerves and enclosing the characteristic blood-spaces of the erectile tissue. Numerous bundles of unstriped muscle, irregularly disposed, occupy the fibrous trabeculæ and plates that separate the venous spaces, which are thus surrounded by imperfect layers of contractile tissue. The trabecular muscle

is most abundant within the cavernous and spongy bodies, and least so within the glans.

The **arteries** conveying blood to the erectile tissue are of two kinds: those coursing within the trabeculæ and nourishing the tissues, **vasa nutritia,** and those carrying blood primarily to the venous lacunæ. The latter are connected with the arteries either directly, by minute channels, or by intervening capillaries. Within the trabeculæ of the deeper parts of the erectile masses, short tortuous branches, **arteriæ helicinæ,** are given off; in the relaxed condition these are twisted and project into the blood-spaces. Both the arteriæ nutritiæ and helicinæ finally directly communicate by minute canals with the deeper lacunæ of the cavernous tissue. The arteries of the

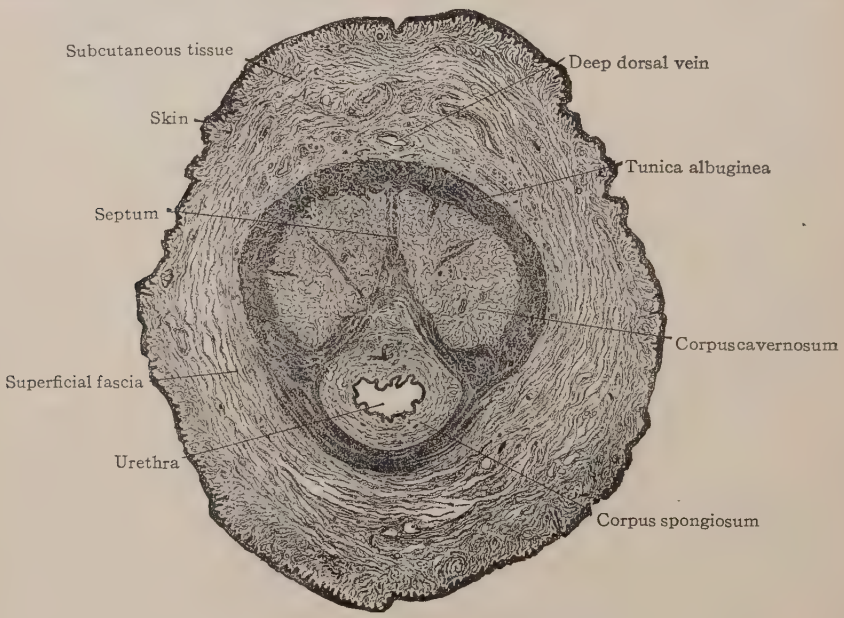


FIG. 293—Transverse section of penis of child. × 10.

erectile tissue are remarkable for the unusual thickness of their circular muscle. In places the intima likewise exhibits excessive thickness due to accumulation of longitudinal muscle, such local augmentations producing cushion-like bulgings that encroach upon the lumina of the arteries.

The **lacunæ**, the blood-spaces that occupy the interstices between the trabeculæ, are regarded as venous networks which communicate with the arteries, on the one hand, and with the radicles forming the veins on the other. Beyond the single layer of lining endothelial plates they possess no special wall. Their form and size depend upon the degree of distention, when containing little blood being often mere slits, or irregular stellate clefts, while when filled they become more cylindrical. Three tracts may be distinguished: (**a**) a narrow **outer peripheral zone** of almost capillary spaces, for the most part narrow and triangular in outline; (**b**) an **inner peripheral**

zone of larger spaces of uncertain form and from .15–.20 mm. in diameter and (c) a **central zone** of still more extensive spaces (1–3 mm.) enclosed by relatively thin lamellæ and trabeculæ. The deep **veins** draining the erectile cylinders do not directly open from the blood-spaces, but are formed by tributaries of various size that begin as apertures in the walls of the lacunæ of which they are extensions. The tributaries of the superficial venous trunks, as the dorsal veins, arise chiefly from the venous networks of the peripheral zone. The veins possess unusually strong muscular coats and exhibit local cushion-like thickenings of the intima, similar to but less marked than those seen in the arteries. The erectile tissue of the corpus spongiosum includes that of the urethral mucosa, produced by the unusual

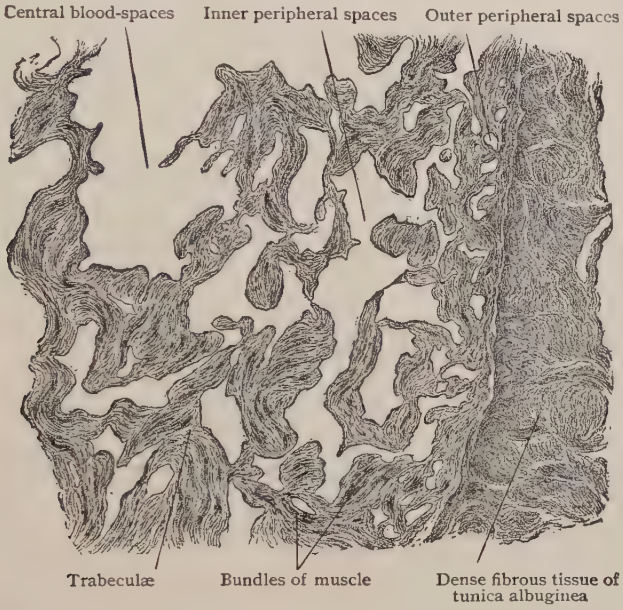


FIG. 294.—Transverse section through periphery of corpus cavernosum, showing erectile tissue. × 50.

abundance of the venous channels, and that of the spongy body proper, a surrounding tract having much the character of the corpora cavernosa. The spongy body is distinguished by the stoutness of its trabeculæ and the small size of its venous spaces; further, by the absence of arteries opening directly into the lacunæ.

The **lymphatics** of the penis are disposed as superficial and deep vessels. The latter are particularly numerous in the periphery of the glans and send tributaries to aid in forming a deep dorsal lymph-stem along the corresponding vein. The superficial lymphatics are directed chiefly to a superficial dorsal trunk that accompanies the superficial vein and begins by the confluence of networks within the integument.

The **nerves** of the penis include both spinal and sympathetic fibres, the former from the ileo-inguinal and the pudic nerves and the latter from the

hypogastric plexus. The integument of the body, glans, and prepuce is supplied by the dorsal nerves. The cylinders of cavernous tissue also receive twigs from the pudic nerves, the bulbar branches of which pass to the bulbus urethræ and in addition supply the mucous membrane of the urethra. Each corpus cavernosum receives a deep branch from the dorsal nerve. The sympathetic fibres, destined for the blood-vessels and unstriped muscle of the erectile tissue, continue from the hypogastric to the cavernous plexus; here, joining the dorsal nerves of the penis, twigs are sent to the corpora cavernosa, some terminating in the spongy body. Close networks of unmyelinated fibres have been followed into the involuntary muscle within the blood-vessels and the trabeculæ of the erectile tissue. Certain cerebro-spinal fibres, known as the **nervi erigentes**, from the third and fourth sacral nerves, are supposed to be especially concerned in erection; they are conveyed in company with the sympathetic fibres, along the paths of the cavernous plexus. In addition to the more usual terminations, the skin of the glans and prepuce is provided with special nerve-endings—tactile corpuscles and genital corpuscles—lying within the papillæ and the Pacinian bodies within the subcutaneous stratum. The path of the sensory impulses lies within the dorsal nerves of the penis.

THE PROSTATE GLAND

The prostate is functionally closely related to the generative organs and is regarded as one of the **accessory reproductive glands,** the others being the bulbo-urethral glands.

The prostate gland resembles in form an inverted Spanish chestnut, the base being attached to the under surface of the bladder and the small end, or apex, directed downwards. It is traversed from base to apex by the urethra, and from behind to the urethra by the ejaculatory ducts. The prostate is a tubo-alveolar gland and made up of three chief components—the connective tissue framework, the involuntary muscle, and the glandular tissue. Of these the glandular tissue constitutes a little more than one half of the entire organ and the connective tissue and the muscle each somewhat less than one quarter.

The connective tissue **framework** includes an external fibro-elastic envelope, the **capsule proper,** and a **median septum** which encloses and blends with the walls of the urethra. Between these denser lamellæ, numerous radiating partitions subdivide the organ into pyramidal lobules occupied by glandular tissue. The involuntary **muscle,** embedded within the capsule and the ramifications of the connective tissue framework, surrounds the gland-substance as a superficial layer, from which a median septum (about 2 mm. wide) extends ventro-dorsally and encloses the urethra in an annular thickening. The interior of the prostate, therefore, is occupied by a dense fibro-muscular core in which the glandular tissue is represented by the narrow prostatic ducts passing towards the urethra. The muscle is not limited to the foregoing positions, but is found between the divisions of the gland-tissue, the interalveolar septa consisting in places largely of the variously disposed muscle-bundles.

The **glandular tissue** embraces from 53 to 74 lobules (average 63 lobules, Lowsley, '12), drained by a like number of tubules, the **prostatic ducts,** that open into the prostatic urethra in the groove on either side of the median elevation, the urethral crest. Beginning at their narrow orifices, the ducts pass outward into the lobules, after a course of about 1 cm. dividing into tubules that repeatedly branch and expand into the terminal alveoli. Throughout the greater part of their course the wavy ducts are beset with saccular and tubular diverticula, simple or compound, that give the canals irregular lumina and constitute the **duct alveoli** as distinguished from the **terminal alveoli.** The latter form a series of irregularly branched tubular and saccular spaces lined with a single layer of columnar epithelial cells, the secreting elements of the gland. The epithelium of the prostatic ducts and

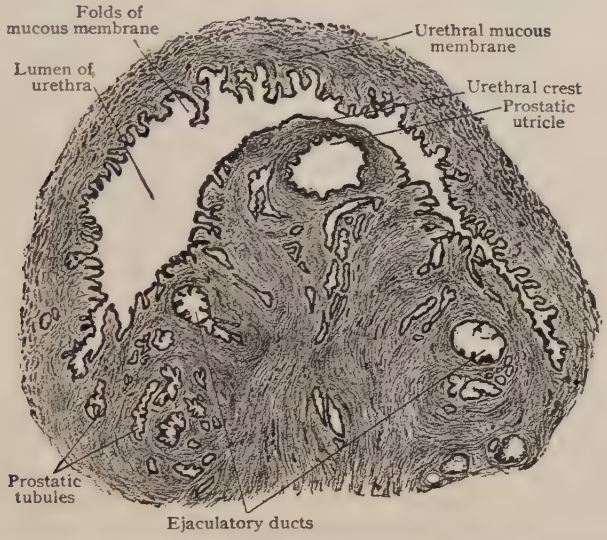


FIG. 295—Section across prostatic urethra, above entrance of ejaculatory ducts, showing urethral crest with prostatic utricle. × 10.

their diverticula corresponds with that lining the terminal alveoli, the change into the transitional variety found in the prostatic urethra not occurring until very near the termination of the ducts.

Peculiar **concretions,** known also as "prostatic calculi" or "amyloid bodies," are almost constantly present within some of the alveoli of the adult organ, especially in advanced life. These bodies (Fig. 297), round or oval in outline and very variable in size (.2–1 mm. and more), usually exhibit a faint concentric striation and a light brownish color. Their nature is uncertain, but they probably consist of modified secretion.

The **secretion** of the prostate gland is turbid, or milky, in appearance, thin in consistence, slightly alkaline in reaction and possesses a characteristic odor. It is discharged into the urethra and mingled with the fluid entering by the spermatic ducts during ejaculation, and probably serves an important purpose in facilitating and perhaps stimulating the motility of the

sperms. The "sperm crystals," formed in semen on standing, and attributed to the products of the prostate, are not found in the prostatic secretion during life, although frequently present in the gland after death.

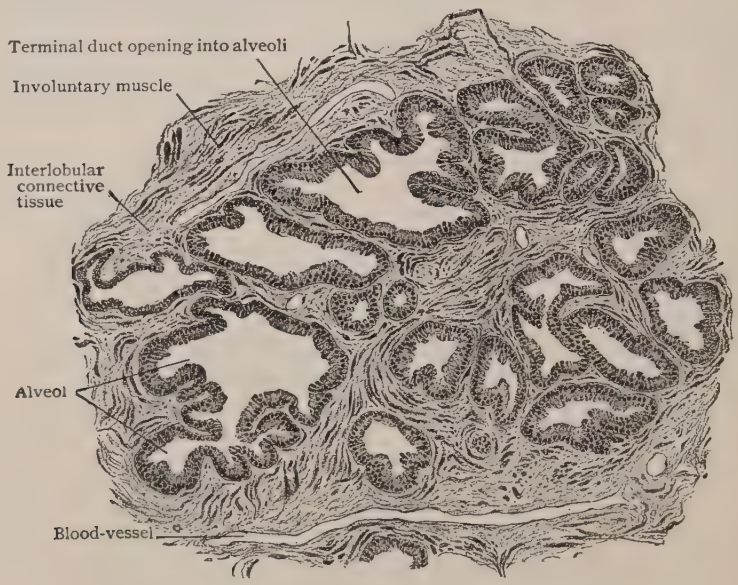


FIG. 296—Transverse section of prostate gland. × 75.

The **blood-vessels** supplying the prostate enter the periphery of the gland at various points, particularly in company with the ejaculatory ducts.

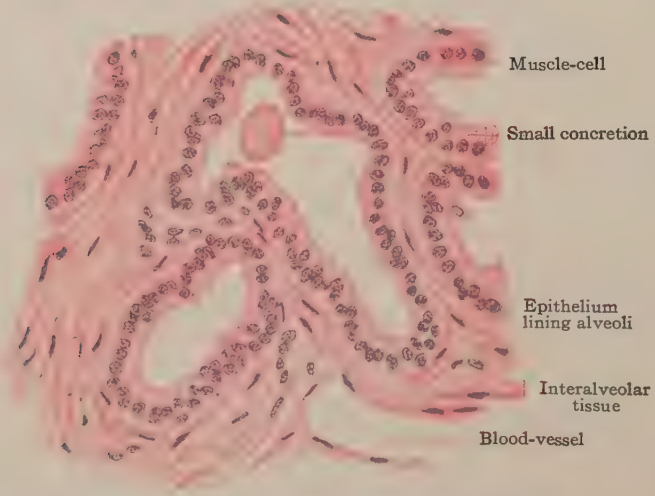


FIG. 297.—Section of prostate gland, showing details of alveoli. × 270.

The interlobular twigs follow the septa and eventually break up into capillary networks that surround the alveoli. The numerous venous radicles form

close meshworks within the glandular tissue and around the ducts. The larger veins leave the deeper parts of the organ on each side and unite into a plexus within the capsule, from which pass emergent trunks.

The **lymphatics** arise in lymph-channels around the alveoli. From the deeper networks stems pass to the surface, where they form a second and superficial network from which efferents course in various directions.

The **nerves** of the prostate are chiefly sympathetic fibres derived from the hypogastric plexus, numerous microscopic ganglia occurring along their course. Their ultimate distribution is largely to the walls of the blood-vessels and to the unstriped muscle, additional fibres being traceable into the glandular tissue, outside the basement membrane of the alveoli. Sensory endings include special terminations in the form of lamellated corpuscles, end-bulbs, and peculiar encapsulated endings, which are modifications of the Pacinian and Krause corpuscles. These peculiar end-organs are found chiefly within the fibrous capsule.

THE BULBO-URETHRAL GLANDS

The bulbo-urethral, or **Cowper's glands,** are two small bodies situated on the under surface of the membranous portion of the male urethra, one on either side of and close to the mid-line. In general form and size (5–8 mm. in diameter) they resemble a pea, although their contour is irregular.

The **ducts** of the glands, about 1.5 mm. in diameter and from 3–4 cm. in length, run forwards and medially and open by small slit-like orifices, often by a common opening on the lower wall of the bulbous part of the spongy urethra. The glands are mucous tubo-alveolar in type, their terminal divisions ending, after more or less branching, in irregularly sacculated compartments. The **alveoli** are lined with low columnar or pyriform cells, among which mucus-secreting elements are plentiful. The cuboidal epithelium that lines the smaller ducts, as well as the dilatations connected with them, is succeeded by columnar cells within the larger ducts until near their termination, where the simple epithelium is replaced by two or more rows of cells. The divisions of the gland are united by intertubular connective tissue and invested by a fibrous envelope, containing a considerable quantity of unstriped muscle intermingled with striated fibres derived from the surrounding compressor urethræ muscle. The **secretion** of Cowper's glands is clear and viscid and of alkaline reaction.

The **blood-vessels** supplying the bulbo-urethral glands, branches from the arteries of the bulb, form capillaries that enclose the alveoli and diverticula. The veins begin in the interalveolar tissue and are tributary to those from the bulbous part of the spongy body. The **lymphatics** arise from networks of lymph-channels in the interalveolar connective tissue and join into efferents to the internal iliac lymph-nodes. The **nerves** are from the pudic and include both myelinated and unmyelinated fibres, the latter being principally from the sympathetic.

THE FEMALE REPRODUCTIVE ORGANS

The reproductive organs of the female include two groups, the internal and the external organs. The **internal organs** are: the sexual glands, the **ovaries,** which produce the female sex-cells, or ova, and also contain organs of internal secretion; the **oviducts,** or **Fallopian tubes,** the canals conveying the ova after these are liberated from the ovaries; the **uterus;** and the **vagina,** the passage which embraces the lower end of the uterus above and ends below within the genital cleft. The oviducts, uterus, and vagina represent the excretory canals of the sexual glands which in the embryo, as the Müllerian ducts, for a time are separate. After fusion of their lower segments has taken place, the unpaired canal thus formed becomes the vagina and the uterus, the latter being a specialized segment for the reception and retention of the fertilized ovum during gestation. The **external organs,** termed collectively the **vulva** (pudendum muliebre) include: the **clitoris,** the **labia,** and the thereby enclosed **vestibule** and **vaginal orifice,** and the **glands of Bartholin.** Although morphologically belonging to the integument, the **mammary glands** may be conveniently considered here, because of their close functional relationship with the reproductive system.

THE OVARIES

The ovary, one on either side, is a solid body, resembling in form a large almond, and in the adult lies against or near the lateral pelvic wall invested by modified peritoneum continued from the posterior surface of the broad ligament of the uterus. That portion of the attached anterior border through which the vessels and nerves enter and emerge is known as the **hilum.** The surfaces of the mature ovary are not even as in early life, but modelled by rounded elevations of uncertain size and number and by irregular pits and scars. The elevations are due to the underlying egg-follicles in different stages of growth, while the scar-like areas indicate the position of regressing corpora lutea which earlier have replaced the ruptured egg-follicles. The average dimensions of the adult ovary are: 36 mm. in length, 18 mm. in breadth, and 12 mm. in thickness. After cessation of menstruation, about the forty-fifth year, the ovary decreases in size and weight, in old women being reduced to one half or less of its previous proportions.

The ovary consists of two principal divisions: the **cortex** (zona parenchymatosa), a narrow peripheral zone, from 2–3 mm. thick, that forms the superficial part of the organ; and the **medulla** (zona vasculosa), that embraces the deeper and more central remaining portion of its substance. The cortex alone contains the characteristic Graafian, or egg-follicles, and the ova, while the medulla is distinguished by the number and size of the blood-vessels, especially the veins.

The Cortex.—Seen in sections of the functioning organ, the cortex appears to consist chiefly of the compact **ovarian stroma,** a modified connec-

tive tissue composed of spindle-shaped cells and fibrous tissue. The **stroma-cells** are arranged in bundles extending in all directions and, hence, are seen cut in different planes. Immediately beneath the modified mesothelium, the so-called **germinal epithelium** that covers the free surface, the stroma is disposed with greater regularity and forms a narrow compact superficial stratum, the **tunica albuginea,** in which the ova are absent. Within the subjacent and looser stroma lie the most characteristic components of the cortex, the **Graafian,** or **egg-follicles.** The follicles are in different stages of development, but, for the most part, are small, inconspicuous, and immature.

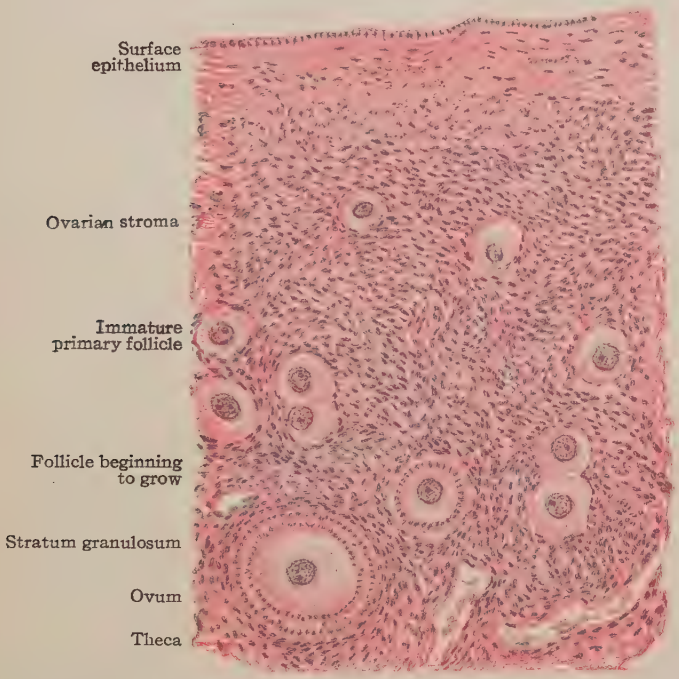


FIG. 298—Section of cortex of ovary of young woman, showing primary and growing follicles within the ovarian stroma. × 190.

Corresponding with their development, the egg-sacs are divided into **primary, growing,** and **maturing follicles.** In general, the youngest and least developed lie nearest the surface, the more advanced deep and towards the medulla, while those approaching full development appear as huge vesicles that may occupy not only the entire thickness of the cortex, but produce marked elevation of the surface. The entire number of ova, as estimated from the ovaries of a seventeen-year-old subject, is approximately 35,000 for both ovaries.

The immature **primary follicles** are microscopic in size (40–60 μ) and, in the ovaries of young adults, form an incomplete and scattered single, or at most double, layer. Each follicle includes the centrally situated young egg, or **ovulum,** surrounded by a single row of flattened epithelial, or **mantle-cells,** which are directly lodged within the interstices of the stroma-tissue. The ova and the mantle-cells are derived from

the proliferation of the **germinal epithelium,** the modified mesothelium covering the germinal ridge on the median surface of the mesonephros. Very early certain cells are distinguished by their exceptional size and large clear nuclei. These are the primary ova, around which the small descendants of the germinal epithelium become arranged as the mantle-cells. Soon an active intergrowth occurs between the proliferating epithelium and the invading vascular connective tissue that becomes the ovarian stroma. The latter increases so rapidly that the primary follicles, single or in small groups, become separated by augmenting tracts of stroma-tissue.

The **primary ova,** approximately spherical and 40–50 μ in diameter, may remain for years, sometimes from early infancy to advanced age, practically unchanged, until they undergo either atrophy, as do most of them, or further growth, leading, under favorable conditions, to the production of mature germ-cells. Of the thousands of primary ova contained within the ovaries just before puberty, a comparatively few

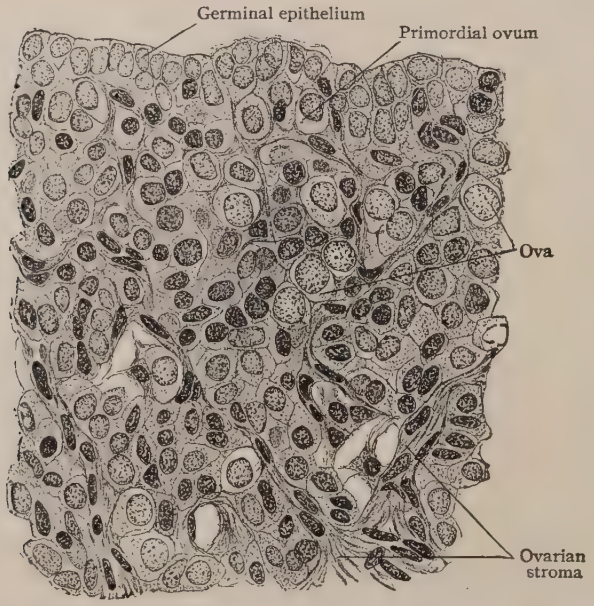


Fig. 299—Section of developing ovary from human embryo, showing intergrowth between derivatives from germinal epithelium and stroma-tissue from Wolffian body. × 560.

attain perfection, between 300–400 probably being the maximum number liberated during the usual period of sexual activity. When enclosing an ovum destined for complete development, the primary follicle enters upon a period of active growth, the flat mantle-cells of the egg-sac changing into a single layer of cuboid epithelium.

The **growing follicles** are distinguished by the rapid proliferation of their cuboid epithelium that results in the production of a stratified **follicular epithelium** surrounding the ovum. Outside this polygonal epithelium, the stroma condenses into a connective tissue envelope, the **theca,** which subsequently differentiates into an **outer** and an **inner tunic,** the former being composed of concentrically disposed fibrous tissue and the latter of round or spindle cells and numerous capillaries. After the formation of the follicular epithelium, the ovum itself begins to grow, the expansion proceeding uniformly and affecting all parts of the cell, including the nucleus and nucleolus. It attains its maximum diameter long before the follicle reaches full growth. Through the activity of the egg itself or of the follicular epithelium the egg becomes invested with a protecting envelope, the **zona pellucida,** or **radiata,** after which little or no further increase in the size of the egg occurs. At first solid, the growing follicle is converted into a

vesicle containing fluid by, at first, the progressive vacuolation and breaking down of the cells of the middle layers of the follicular epithelium and, later, by the transudation from the surrounding blood-vessels. This fluid, the **liquor folliculi,** increases to such

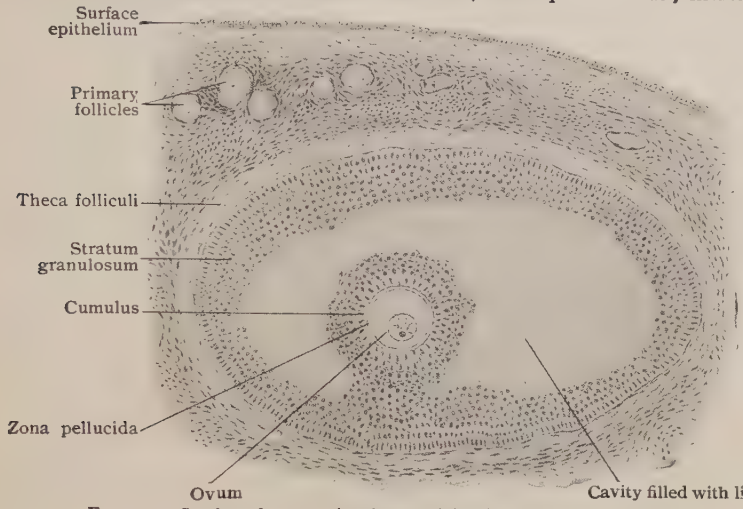


FIG. 300—Section of ovary, showing partially developed Graafian follicles. × 90.

an extent that it soon occupies the greater part of the expanding egg-sac, now entering upon its final stage of growth. The liquor folliculi contains an important ovarian hormone, or internal secretion (Allen, '24). Injections of the fluid into spayed animals induce the accelerated growth, hyperemia, and secretion in the genital tract characteristic of the period of œstrus. The investigation of its properties is still in active progress.

The **maturing follicles,** also known as **vesicular,** occupy the deeper parts of the cortex and reach to the medulla. With their continued expansion they appropriate more and more of the cortex, until the entire thickness of the latter and, sometimes, part of the medulla are occupied by the ripe follicle, which just before its rupture attains a diameter of from 1–2 cm. and models the free surface of the ovary as a tense rounded elevation. After rupture and liberation of the ovum, the follicle becomes filled by a new growth of cells, derived from the follicular wall and called a **corpus luteum.**

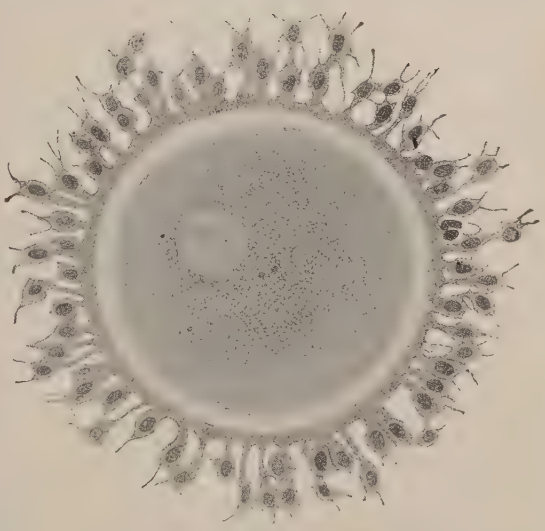


FIG. 301—Almost mature human ovum taken from fresh ovary. Ovum, with germinal vesicle and spot, is encircled by clear zona pellucida, which is surrounded by follicular epithelium. × 250. (*Waldeyer.*)

The wall of the **ripe follicle** consists of a well-developed capsule, or **theca,** a delicate **membrana propria,** against whose inner surface lie the follicular cells, known as the **stratum granulosum,** surrounding the space filled with the liquor folliculi. Opposite the point where rupture takes

place, the stratum granulosum is prolonged into a pedunculated spherical mass of epithelial cells that projects into the cavity. This mass, the **cumulus ovigerus,** encloses the ovum and on section appears as an epithelial ring that encircles the zona pellucida and the ovum and consists of two or three layers of cells. The innermost layer is radially disposed and constitutes the **corona radiata.** The membranous **zona pellucida** is in some cases the product of the ovum; it sometimes exhibits a radial striation, hence is also called **zona radiata.**

The **human ovum** when about to be liberated from the Graafian, or egg-follicle possesses a diameter of about .25 mm. Its cytoplasm, the **vitellus** of the older writers, exhibits differentiation into a peripheral **ooplasmic** and

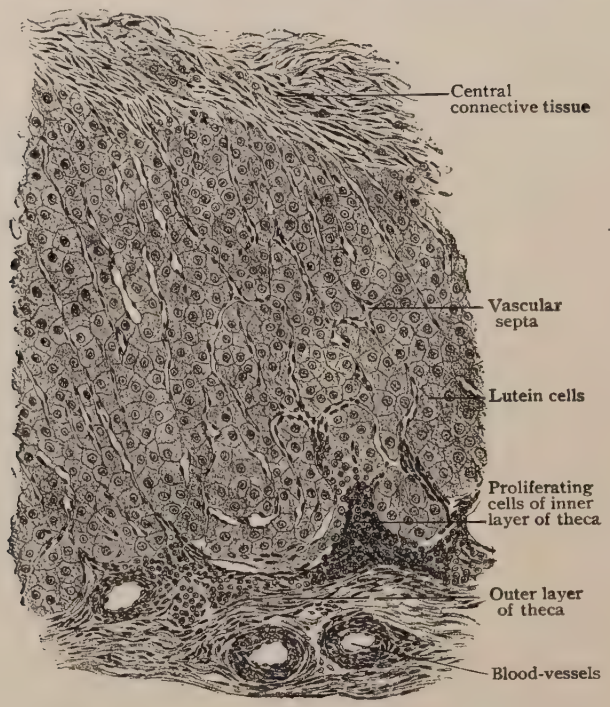


FIG. 302—Section of human corpus luteum. × 70.

a central **deutoplasmic** zone, the latter being dark and conspicuous on account of the irregular refraction of the enclosed yolk-particles. The presence of a distinct cell-wall, or **egg-membrane,** in the human ovum is doubtful, although demonstrable in some mammals. The spherical egg-nucleus, the **germinal vesicle,** lies eccentrically placed within the deutoplasmic zone and measures from 30–45 μ. It is bounded by a sharply defined nuclear membrane and contains the nucleolus, or **germinal spot** (4–8 μ), and the nuclear reticulum.

Corpus Luteum.—When the follicle approaches maturity, the inner layer of the theca becomes the seat of great activity, the blood-vessels increasing and the cells undergoing rapid proliferation and extraordinary growth, the enlarged elements becoming filled with a yellowish substance and transformed into **lutein cells.** Coincidently

the follicular epithelium suffers fatty change which results in the partial disintegration of the cumulus and freeing of the ovum, enclosed by the cells of the corona radiata, into the cavity of the follicle. When the latter ruptures the expulsion of its contents is followed by hemorrhage into the cavity of the follicle and, soon afterwards, by closure of the opening in the sac. The position of the rupture corresponds to the place (**stigma**) where the wall of the follicle is most distended and least vascular and, hence, possesses least vitality and resistance. The rapid proliferation and growth of the lutein cells derived probably from both theca interna and stratum granulosum produces an irregularly plicated wall of increasing thickness that invades the hemorrhagic mass. The latter is gradually absorbed until the encroaching projections of lutein cells and invading vascular connective tissue meet and the cavity of the follicle is obliterated, its former position being subsequently indicated by a central core of connective tissue. The complex thus formed, composed of lutein cells and septa of vascular connective tissue, is the **corpus luteum.**

When the liberated ovum becomes fertilized, the corpus luteum grows to huge dimensions and forms a conspicuous oval mass that may approach 3 cm. in length and occupy a considerable part of the entire cortex. When associated with pregnancy it

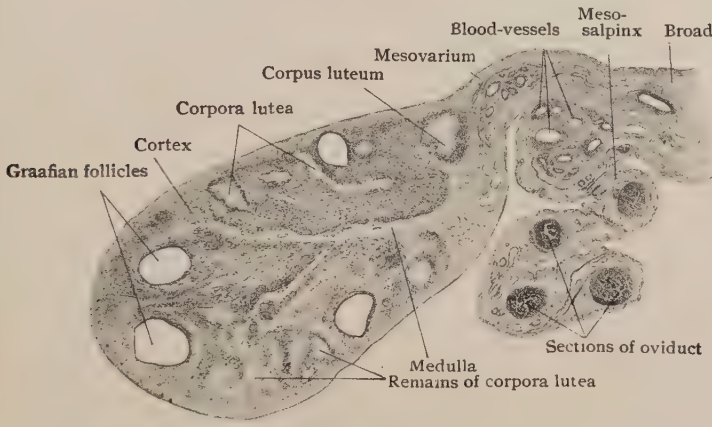


FIG. 303—Cross-section through ovary, oviduct and part of broad ligament. × 4.

is termed the **corpus luteum verum.** If impregnation does not occur, the yellow body, now called the **corpus luteum spurium,** is smaller and seldom exceeds from 1.5–2 cm. The classic distinction of "true" and "false" has some anatomical basis, since they show certain cytological differences (Corner). The assumption, that the presence of a large corpus luteum is proof of pregnancy, must be accepted with much caution, since yellow bodies of unusual size are sometimes observed in ovaries of virgins. With the production of a solid corpus luteum and the absorption of the blood, evidences of the latter remaining for a long time as hematoidin crystals, the active rôle of the lutein cells is finished. These elements now lose their yellow pigment (**lutein**), undergo fatty change, and finally entirely disappear. The connective tissue which now constitutes the entire mass, undergoes hyaline change, becoming clear and nonfibrous, while the ageing corpus luteum loses its former appearance and is transformed into an irregular body, light in color and sinuous in outline, sometimes termed the **corpus albicans.** The corpus luteum is now regarded as an organ of internal secretion, which produces a stimulant of the uterine mucosa for the formation of the deciduæ, and of the mammary gland.

The Medulla.—The vascular central zone of the ovary, the medulla, consists of comparatively loose stroma-tissue, composed of irregularly felted bundles of fibrous tissue rich in elastic fibres, supporting the vessels and nerves. In the mature ovary, with the exception of occasional encroaching

Graafian follicles that are ripening, egg-sacs are not found within the medulla. The larger vessels of the medulla are surrounded by considerable tracts of

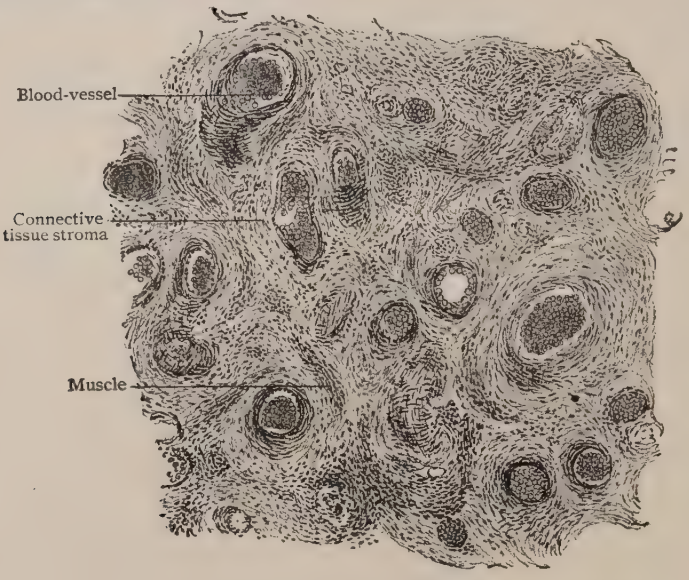


FIG. 304—Section of medulla of ovary, showing numerous blood-vessels and fibro-muscular stroma. × 75.

involuntary muscle, which are continuous in part with those of the utero-ovarian ligament, through the hilum and mesovarium, the fold of peritoneum which attaches the ovary to the broad ligament. The veins are particularly large and appear in sections as huge blood-spaces of irregular outline, in consequence of their tortuosity and plexiform arrangement.

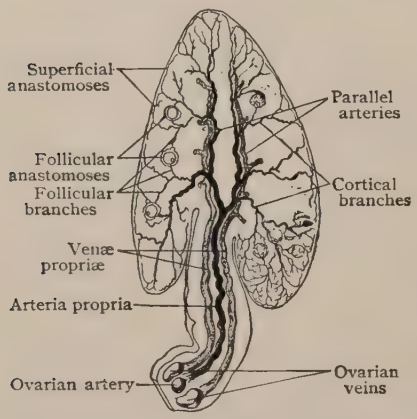


FIG. 305—Diagram illustrating arrangement of ovarian blood-vessels. (*Clark*)

The **blood-vessels** supplying the ovary are four or five branches from the anastomatic arch formed by the ovarian and uterine arteries. These branches, the **arteriæ propriæ**, reach the medulla through the hilum as closely grouped tortuous vessels. On gaining the interior of the ovary, each stem divides into two **medullary** or **parallel arteries** that proceed directly towards the opposite free margin of the organ, lying just beneath the cortex to which they distribute **cortical branches** at regular intervals. In their course towards the periphery the cortical branches supply hundreds of **follicular twigs** to the egg-sacs, each of the latter being provided with a rich vascular network that anastomoses

with two or more follicular twigs. At the periphery of the organ, the blood within the cortical arterioles reaches the veins through an intervening capillary network. The **veins** follow the general arrangement of the arteries in the cortex and medulla; the pairs of parallel veins, however, do not unite into single stems, but emerge from the hilum as independent trunks.

The **lymphatics** begin in the cortex as networks and from these radicles the larger and irregular channels enter the medulla, where they form converging stems that follow the blood-trunks and leave the hilum as 7–9 trunks.

The **nerves** supplying the ovary are from the sympathetic plexus surrounding the ovarian artery, and are composed, for the most part, of unmyelinated fibres. They accompany the arteries through the hilum into the ovary and are distributed chiefly to the walls of the blood-vessels, around the larger of which the terminal plexuses are formed. From the fairly close cortical plexus twigs pass to the larger follicles, the ultimate relation between the latter and the surrounding fibres being uncertain. It is probable, however, that the fibrils end mostly in the walls of the follicular blood-vessels, although some are said to penetrate to the follicular epithelium. The existence of sympathetic ganglia within the medulla has not been established.

THE OVIDUCTS

The oviduct, or **Fallopian tube,** also called the **tuba uterina,** is, in principle, the excretory canal of the sexual gland, since it conveys the ova liberated from the ovary to the uterus, into which it opens. The relation between the ovary and its duct is exceptional, in that these organs are not continuous but only in apposition, the ova liberated from the ruptured Graafian follicles finding their way into the expanded end of the oviduct. The entire length of the tube is about 11.5 cm. (4½ in.), its diameter increasing from 3–4 mm. at the **isthmus,** next the uterus, to from 6–8 mm. at the outer limit of the **ampulla,** where the canal suddenly expands into the terminal trumpet-shaped **infundibulum.** The mucous membrane lining the oviduct is thrown into longitudinal folds, which become progressively more marked towards the outer end, so that cross-sections of the ampulla present a lumen of complex outline owing to the projection of primary and secondary plications. At the irregularly notched, or fimbriated, margin of the infundibulum, the mucous lining of the tube is directly continuous with the peritoneum. The exceptional relation of the tubal mucosa to the serous membrane, this being the only place in the body where a mucous tract directly communicates with a serous sac, is a persistence of the similar relation of the embryonal Müllerian duct, from which the oviduct is directly derived.

The **wall proper** of the oviduct consists of the **mucous** and **muscular coats** and is embedded within the loose connective tissue of the broad ligament (**tunica adventitia**), and surrounded by the **serous coat,** which completely invests the duct with the exception of the narrow interval through which the tubal vessels and nerves pass. The wall is thickest and firmest

in the isthmus, less so in the ampulla and thinnest and most relaxed in the infundibulum and fimbriæ. The mucous coat is thrown into longitudinal folds, which in the ampulla attain much complexity and in transverse sections appear as branching villus-like projections.

The **mucous membrane** is covered by a single layer of columnar epithelium provided with cilia, whose current is directed towards the uterus, thus favoring the progress of the ova along the tube, but retarding the ascent of the spermatozoa. The tunica propria consists of bundles of fibrous tissue, is rich in cells and directly continuous with the intermuscular connective tissue. Its deepest layer often contains irregular strands of muscle-bundles, which suggest a muscularis mucosæ. The **muscular coat,** upon which the

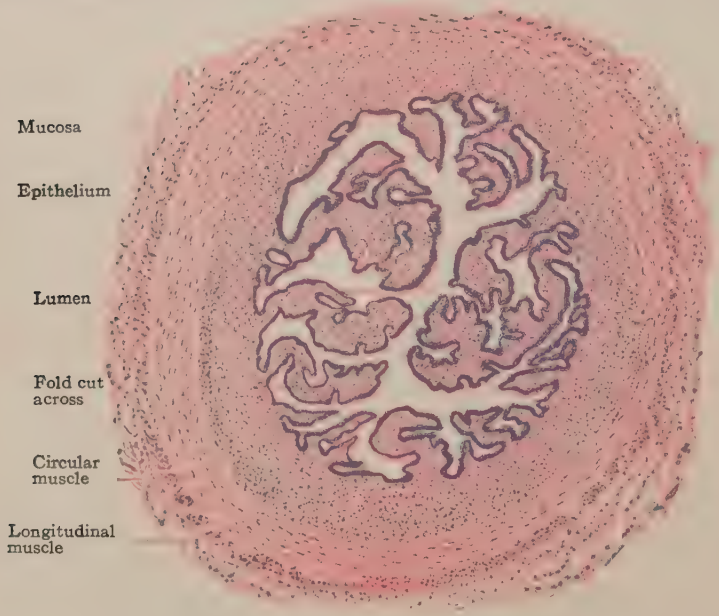


FIG. 306—Transverse section of oviduct near outer end of ampulla. × 35.

mucosa rests without the intervention of a submucous layer, is most robust towards the uterus and thinnest at the infundibulum. It includes an inner circular and an outer longitudinal layer of unstriped muscle. At the isthmus, where the firmness of the tubal wall depends chiefly on the muscular coat, the circular layer is the thicker (.5–1 mm.) and the longitudinal one is incomplete; towards the infundibulum the reverse is true, the longitudinal layer being better developed and the circular muscle reduced to .2 mm. or less. The surrounding fibrous tissue, sometimes described as a distinct coat, the **tunica adventitia**, blends with the fibro-elastic stroma of the investing peritoneum, which may be regarded as the **serous coat.** These structures consist of the usual connective tissue and mesothelial elements of peritoneum.

The **blood-vessels** supplying the oviduct are derived from the tubal branches of the uterine and ovarian arteries. They gain the wall of the tube

between the two layers of the broad ligament and break up into numerous branches between the outer and inner muscular layers, from which capillaries pass to the muscular tissue and to the mucous membrane. The veins begin within the mucosa and join the many intermuscular channels from which tributaries pass to the subserous meshwork. The **lymphatics,** after emerging from the wall of the tube within which they begin as irregular channels between the fibrous bundles of the muscular coat, form three or four stems that accompany the blood-vessels. The **nerves** are numerous, chiefly sympathetic fibres from the ovarian and the uterine plexus. Within the subserous tissue they form a peritubal plexus, from which twigs penetrate the wall of the canal to supply chiefly the involuntary muscle, some fibres entering the mucosa.

THE UTERUS

The uterus, or womb, is a hollow pear-shaped muscular organ, which receives the oviducts above, one on either side, and opens into the upper part of the vagina below. In the uterus the fertilized ovum is retained and develops, and from it the resulting fetus is expelled at the completion of gestation. It measures about 7 cm. in length, of which the lower 2.5 cm. constitutes the neck, or **cervix,** and the remainder the **body;** its greatest breadth is about 4 cm. and its thickness 2.5 cm. The convex upper extremity of the organ is known as the fundus. Of the two surfaces, the anterior is only partially and the posterior almost completely covered with peritoneum.

The uterine wall is thickest at the fundus and posterior aspect of the body, where it measures 1–1.5 cm., and somewhat thinner (8–9 mm.) at the entrance of the oviducts and in the cervix. It comprises three coats—the mucous, the muscular, and the serous. The **mucous coat,** or **endometrium,** is .5–1 mm. thick and consists of a tunica propria of fibrous tissue containing a large number of cells, and the surface epithelium. The latter is a single layer of columnar cells, about 28 μ high, that in their typical condition possess cilia producing a current towards the cervix. The cilia however, are neither always present nor uniformly distributed, since they are lost during menstruation and often present only in patches.

The **uterine glands** are simple tubular or slightly bifurcated wavy invaginations lined with a single layer of columnar cells resembling those covering the adjacent uterine mucosa. They are distributed at fairly regular intervals and extend the entire thickness of the mucosa, their tortuous blind extremities lying close to the subjacent muscle, since a submucosa is wanting. At the orifices of the oviducts, the uterine mucosa becomes thinner, the epithelium lower, and the glands shorter and fewer, until they finally disappear, glands being absent in the tubal mucous membrane.

The mucous membrane of the **cervical canal,** is somewhat thicker and denser than that lining the body of the uterus, but the change is gradual and without definite demarcation. The single-layered columnar cells vary, in some places being taller (40–50 μ) than those lining the body, in others lower and more cuboidal. In addition to tubular crypts in the upper part which although larger resemble those in the body, the cervix contains

cervical glands, wide diverticulated mucous alveoli producing a clear peculiarly tenacious secretion. When the latter is retained, the glands are converted into cysts that appear as minute vesicles and were formerly known as the **ovula Nabothi.** The abrupt transition of the columnar epithelium of the cervical canal into the stratified squamous cells covering the vaginal portion of the uterus takes place, before pregnancy has occurred, at the inner border of the external orifice. After the changes incident to pregnancy have affected the uterus, this transition lies higher, approximately the lower

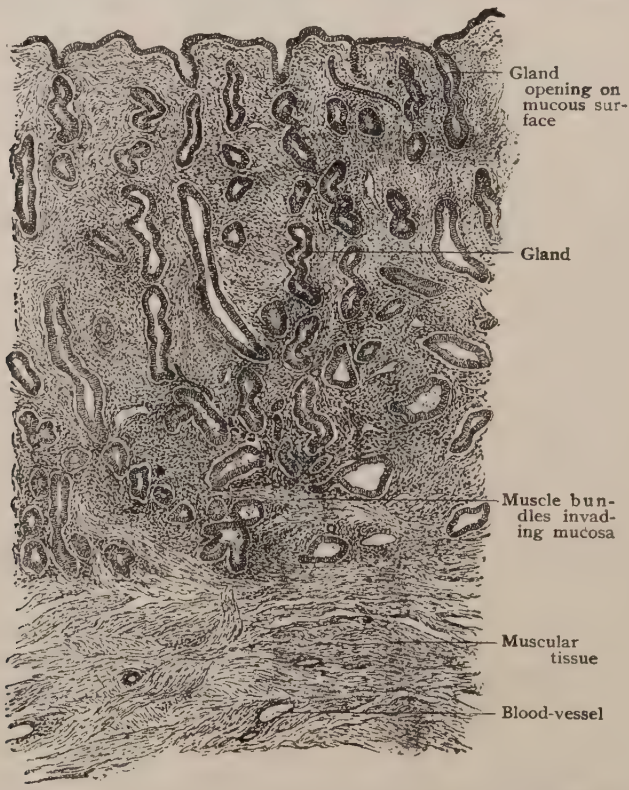


FIG. 307—Section of mucous membrane of uterus, showing glands cut in various planes. × 40.

half of the cervical canal then being clothed with the squamous epithelium.

The **muscular coat,** or **myometrium,** is composed of bundles of involuntary muscle arranged with little regularity; it is possible, however, to distinguish two general strata—a robust **inner layer,** in which the bundles possess a circular disposition, and a thin imperfect **outer layer,** whose component bundles are for the most part longitudinal. The innermost bundles of the circular layer are oblique and longitudinal and sometimes described as a distinct submucous layer. The thick circular layer, the chief component of the myometrium, is distinguished by the number and size of the venous channels that traverse the intermuscular connective tissue;

hence its designation as the **stratum vasculare.** At the orifices of the oviduct and the internal cervical opening, the disposition of the muscle-bundles suggests a sphincter. The longitudinal muscle is most distinct over the fundus and body, being unrepresented in the cervical segment. Here the circular and oblique bundles are intermingled with a considerable quantity of fibro-elastic tissue, an arrangement conferring greater resistance and hardness upon the cervix. The longitudinal muscle-bundles are continued beyond the uterus into the oviducts and the broad, round, ovarian and utero-sacral ligaments. The component fibre-cells of the uterine muscle vary in form, in some places being short and broad and in others long and fusiform.

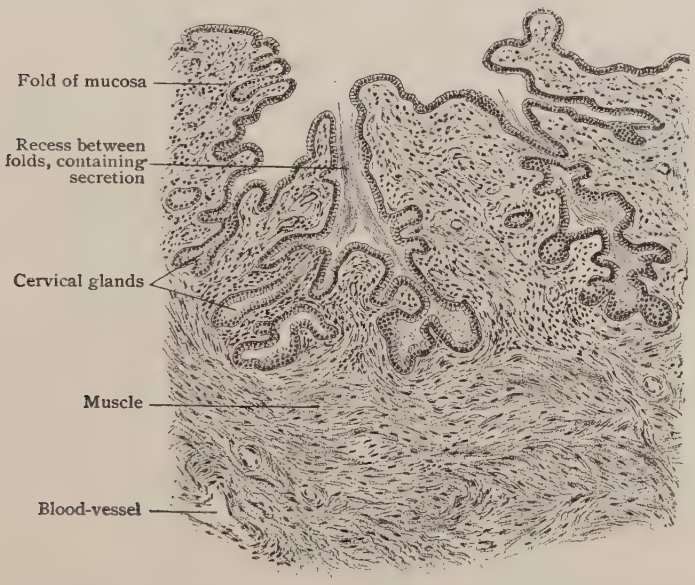


FIG. 308.—Longitudinal section of cervical mucous membrane, showing glands opening into recesses between the plicæ. × 50.

The **serous coat,** or **perimetrium,** continuous laterally with the peritoneal investment of the broad ligament, is closely adherent to the uterine muscle over the fundus and adjacent parts of the anterior and posterior surfaces.

The **blood-vessels** approach the uterus between the layers of the broad ligament. On gaining the muscular coat, the larger branches divide into twigs that penetrate the outer layer of the myometrium and within the circular muscle break up into tortuous branches which in part pass to the mucous membrane and, in conjunction with the large veins, confer a highly vascular character to the stratum. Within the mucosa the capillaries surround the glands and form a network beneath the epithelium. The **veins** begin in the mucosa, but within the middle of the muscular coat form large tortuous channels, sections of which appear as conspicuous irregular spaces between the muscle-bundles.

The **lymphatics** within the mucosa are represented by a network of channels, from which stems pass through the muscular coat to join the close-meshed subserous network of larger lymphatics. The efferent trunks pursue various courses and communicate with the lymphatics of the neighboring organs—vagina, rectum, ovaries, and oviducts.

The **nerves** of the uterus are abundant and include both sympathetic and spinal fibres, unmyelinated and myelinated. Since their chief destination is the involuntary muscle and blood-vessels, the unmyelinated fibres are associated with minute terminal ganglia from which the terminal filaments pass to the myometrium. Other fibres reach the mucosa, within which a close subepithelial plexus is formed, fibrils probably entering the epithelium.

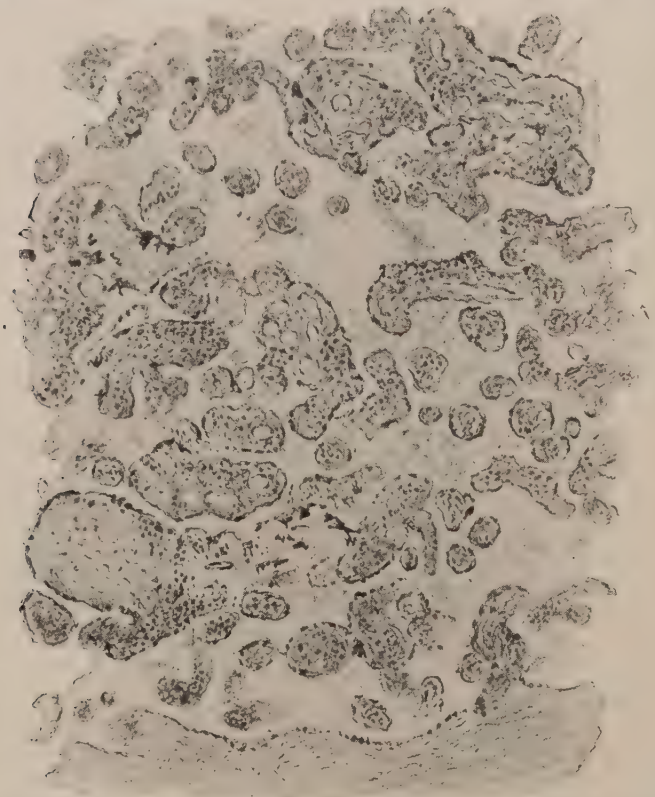


FIG. 309—Human placenta. Within the chorionic villi are fetal blood-vessels, and between them are maternal blood-sinuses. × 144.

Changes During Menstruation and Pregnancy.—The uterine changes occur regularly, every twenty-eight days, when the ovaries are functionally active. In anticipation of the possible reception of a fertilized ovum, the uterine mucous membrane becomes swollen, excessively vascular and hypertrophied, with conspicuous enlargment of the subepithelial blood-vessels and the glands. The resulting thickened and modified mucosa, now from 6–7 mm. thick, offers a soft velvety surface favorable for the implan-

tation of the embryo-sac. Should this occur, the hypertrophy proceeds, and the lining of the uterus is converted into the deciduæ and takes an important part in the formation of the placenta. If, on the contrary, fertilization does not occur, the proliferative processes are arrested and the hypertrophied mucosa, now called the **decidua menstrualis,** enters upon regression. Incidental to the latter are subepithelial extravasation and rupture and partial destruction of the epithelium, followed by the characteristic discharge

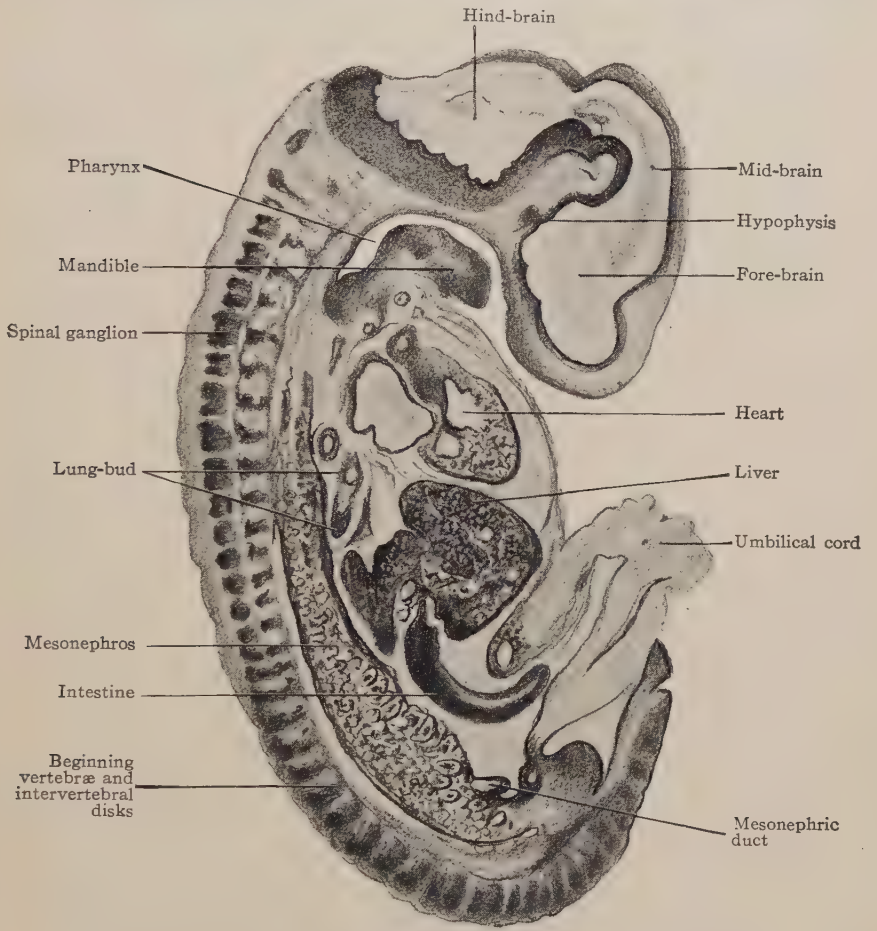


FIG. 310—Pig embryo 12 mm. long, sectioned in the sagittal plane, showing the larger organs. × 10.

of blood. While usually the destruction of the mucosa is limited to the epithelium, it is probable that at times the superficial layer of the subjacent tissue is involved.

During pregnancy the most conspicuous changes are occasioned by the growth necessary to accommodate the rapidly augmenting volume of the uterine contents, by the provision of an adequate source of nutrition and protection for the fetus, and by the development of an efficient contractile apparatus for the expulsion of the same. The enormous increase depends especially upon the hypertrophy of the muscular coat, which during the first half of pregnancy becomes greatly thickened, but later thinner and membranous owing to stretching. The increase results from both the growth of the previously existing muscle-cells and, during the first half of pregnancy,

the development of new muscle-elements. The individual cells may increase tenfold in length and measure between .4–.5 mm. During the first five months, the mucous membrane of the body also becomes greatly hypertrophied, in places attaining a thickness from 7–10 mm. The glands and blood-vessels, particularly the arteries, enlarge and within the specialized area are concerned in the formation of the placenta. The cervical mucosa takes no direct part in the formation of the deciduæ, although it thickens and is the seat of enlarged glands that secrete the plug of mucus that for a time occludes the mouth of the uterus. After the termination of pregnancy, the uterus enters upon a period of involution and repair, the excessive muscular tissue undergoing degeneration and absorption and the lacerated mucosa regeneration, the latter process being completed in from three to four weeks.

THE VAGINA

The vagina is a flattened muscular tube, lined with mucous membrane, that extends from the genital cleft enclosed by the labia below to the uterus above. Its walls, from 2–3 mm. thick, include a mucous and a muscular coat, supplemented externally by a less definite fibrous tunic.

The **mucous coat** consists of stratified squamous epithelium and a

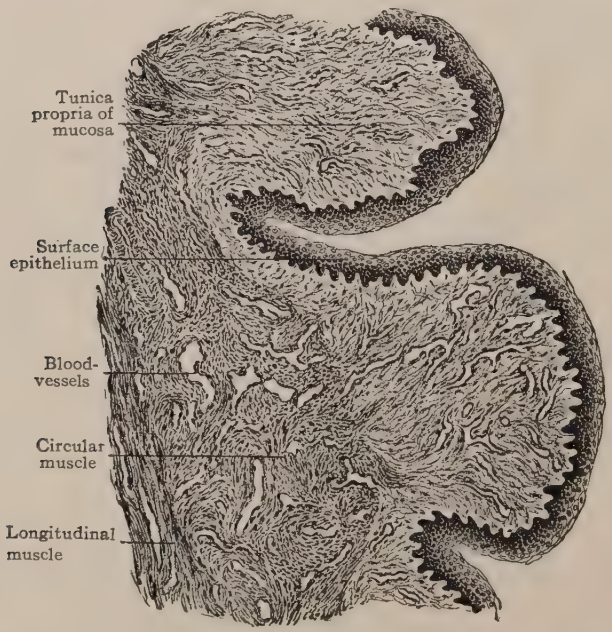


FIG. 311.—Section of wall of vagina, showing the rugæ cut across. × 80.

fibro-elastic tunica propria, exceptionally rich in veins and colorless blood-cells and beset with numerous conical papillæ that encroach upon the overlying epithelium, but do not model the free surface. Although normally moistened by a thin mucous secretion of acid reaction, the vagina is devoid of glands. Small lymph-nodules are scattered through the mucosa, especially in the upper part of the canal. The **hymen,** the membranous fold

partly occluding the vaginal orifice, consists of a basis of vascular fibrous tissue covered by a prolongation of the mucous membrane.

The **muscular coat,** which supports the mucous membrane without the intervention of a distinct submucous layer, is composed of bundles of unstriped muscle arranged, although not with precision, as an inner circular and an outer longitudinal layer. The latter is best developed over the anterior vaginal wall, from which strands of muscular tissue are continued into the urethro-vaginal septum. Behind, bundles are prolonged into the recto-vaginal partition; above the vaginal muscle is continuous with that of the uterus and below penetrates the perineal body. Within the conspicuous elevations, the **columnæ rugarum,** marking the vaginal wall, both mucous and muscular coats are thickened, the elevations acquiring somewhat the character of erectile tissue owing to the abundance of veins intermingled with irregularly disposed muscle-bundles. The **fibrous coat,** outside the muscular, is composed of closely felted bundles of fibrous tissue and plentiful elastic fibres.

The **blood-vessels** supplying the vagina, derived from several sources, form a network between the mucous and muscular coats from which some twigs pass to the muscle and others enter the mucosa where they break up into a capillary network. The veins are very numerous, and unite into a close plexus within the muscular tunic, from which large emergent trunks extend along the sides of the canal.

The **lymphatics** are numerous and represented by an exceptionally close network within the mucosa, one less dense within the muscular coat and a superficial network over the exterior from which the larger main efferent stems arise.

The **nerves** of the vagina are chiefly sympathetic efferents, associated with minute ganglia as they traverse the fibrous coat, for the supply of the blood-vessels and involuntary muscle. The sensory fibres distributed to the mucous membrane lining the upper part of the vagina are meagre, the pudic nerves endowing the mucosa of the lower third of the canal with greater sensibility. Sensory nerve-endings of different kinds have been observed within the mucous membrane.

THE EXTERNAL ORGANS

The **labia majora** are rounded cutaneous folds, the homologue of the scrotum, the integument covering the outer surface being thick, dark-hued, and beset with large hair-follicles. That covering the medial surface is much more delicate in texture, with few and minute hairs. Sweat- and sebaceous glands are numerous. In addition to the investment of skin, each labium majus contains a layer of subcutaneous fat, between which and the integument lies a thin stratum of involuntary muscle, **tunica dartolabialis,** continued forwards from the dartos of the perineum. The centre of the labium is occupied by a fairly well-defined mass of fat, the **corpus adiposum,** that is separated from the subcutaneous tissue by a delicate fibro-elastic membrane.

The **labia minora,** or **nymphæ,** are thin folds of delicate skin continuous with the greater labia at the bottom of the interlabial groove, on the one hand, and with the mucous membrane lining the vestibule on the other. Although both surfaces are covered with integument, the protection and contact with the vaginal secretions to which the median aspect of the fold is subjected, modify the skin on the inner side so that it assumes the color and appearance of a mucous membrane. The line of transition into the vestibular mucosa follows the medial attachment of the fold. The absence of mucous glands and the presence of sebaceous follicles on both surfaces are differential characteristics of skin as contrasted with the adjacent mucous membrane. In addition to the two cutaneous layers, the nymphæ are

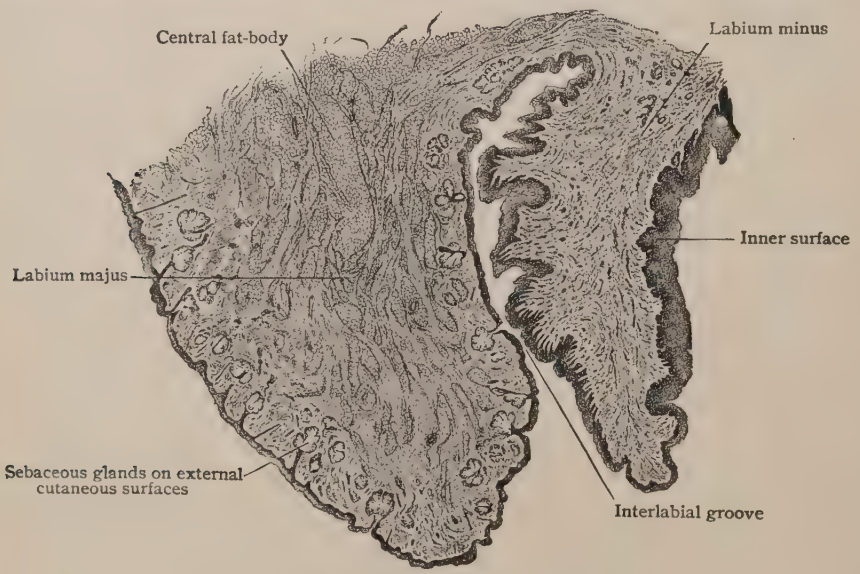


FIG. 312—Section across the labia of young child. × 18.

composed of an intermediate stratum of loose connective tissue, rich in blood-vessels and bundles of unstriped muscle that resembles erectile tissue. Hairs and fat are entirely wanting on the labia minora, but sebaceous and sweat-glands are plentiful after the first few years.

The **vestibule,** the space enclosed by the nymphæ is lined with mucous membrane covered by stratified squamous epithelium and containing many mucous glands. Close to the posterior margin of the urethral orifice, or on the papilla that usually marks this opening lie the small apertures of the **paraurethral ducts.** These canals, also known as the **tubes of Skene,** are from 1–2 cm. long, lead into smaller groups of branched tubules, which are regarded as the homologues of the prostatic tubules. The ducts are lined with stratified squamous epithelium for a short distance from the vestibule, the remainder of the passage and its subdivisions being clothed with columnar cells.

The **glands of Bartholin,** the largest of the vestibular and the homologues of the bulbo-urethral (Cowper's glands,) are two small organs, 1–1.5 cm. in length, situated one on either side of the vaginal orifice. They are tubo-alveolar mucous in type and produce a whitish viscid secretion. The small component lobules are separated by considerable tracts of fibro-muscular tissue and lined with columnar epithelium containing many mucus-bearing cells. The lobular ducts unite to form the single excretory canal, which is beset with minute mucous follicles. The main duct, sometimes provided with an ampullary dilatation, is lined with columnar epithelium until near its termination, where the epithelium becomes stratified squamous to correspond with that of the vestibule.

The **clitoris,** the homologue of the penis, possesses in reduced and modified form the chief components of the male organ. It consists essentially of two miniature corpora cavernosa and an imperfectly developed and cleft corpus spongiosum, known as the **bulbus vestibuli.** The latter consists of two converging elongated masses of cavernous tissue—a complex of tortuous veins and fibro-muscular tissue. The glans and cavernous bodies repeat, although in less typical manner, the histological details described in connection with the corresponding parts of the male.

THE MAMMARY GLANDS

Although morphologically modified cutaneous glands, and developed in both sexes, the functional importance of the mammary glands, or **mammæ,** in the female entitles them to be regarded as organs accessory to the reproductive apparatus.

Each mamma, or breast, comprises a group of some twenty individual and separate glands, opening on the nipple by independent ducts, that collectively constitute the secreting organ, the **corpus mammæ,** as distinguished from the enveloping fat and areolar tissue. Prior to the changes incident to pregnancy the secretory tissue is relatively meagre and overshadowed by the connective tissue in which the ducts and still rudimentary alveoli are embedded.

The **corpus mammæ** consists of from 15–20 or more flattened pyramidal **lobes,** radially disposed with the bases directed towards the periphery and the efferent canals, the **lactiferous ducts,** converging towards the nipple upon which they open. Each lobe is subdivided by connective tissue into several **lobules,** which in turn are made up of the ultimate divisions of the secreting tissue, the **alveoli.** The walls of the latter consist of a membrana propria, lined, in the resting condition, by a double layer of cells. Those next the membrana propria are flat and inconspicuous. They are sometimes called basket-cells and are possibly muscular in nature. The inner cells, the secretory elements, are cuboid or low columnar.

During lactation, the alveoli become greatly enlarged and distended and the intervening connective tissue correspondingly reduced so that the alveoli are pressed close together. The cytoplasm of the cells engaged in the production of milk contains minute oil droplets, which, as they increase

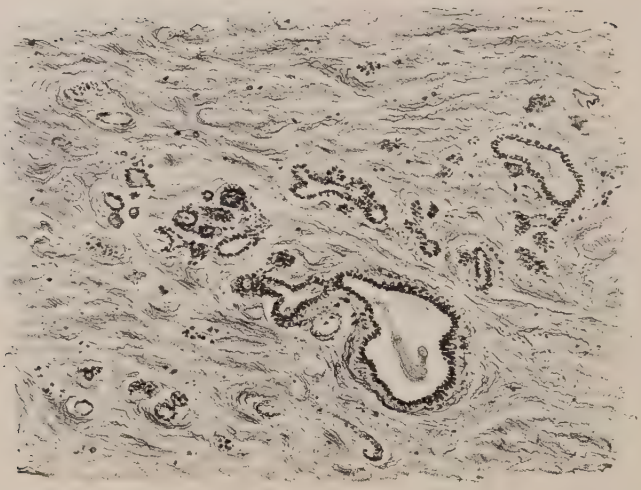


FIG. 313—Functional Variations in the Mammary Gland: *A*,—at third month of gestation; no well-developed lobules, but scattered glandular elements. × 90. (*Preparation by Professor McFarland*)

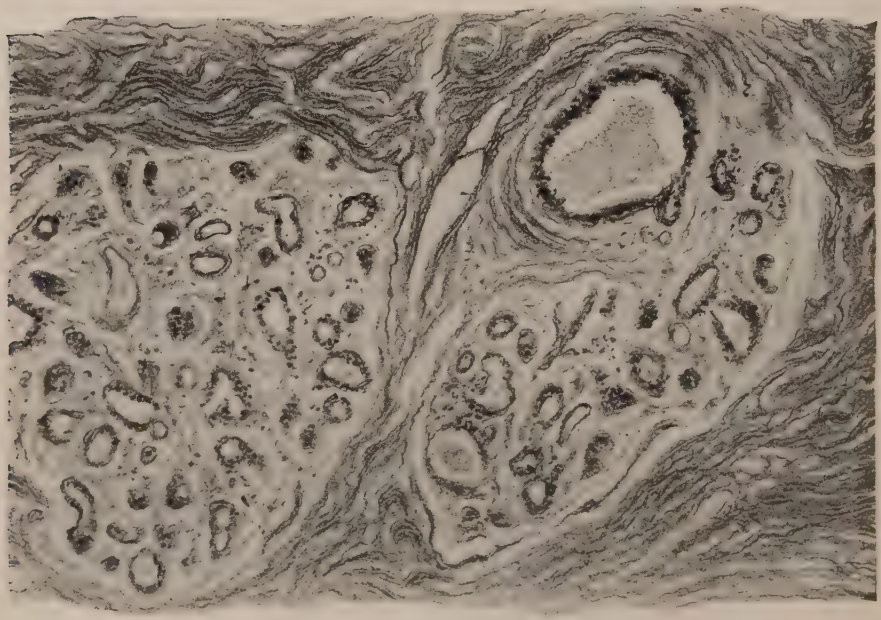


FIG. 313*B*—At ninth month of gestation; distinct lobules and well developed intralobular fibrillar tissue. × 90. (*Preparation by Professor McFarland*)

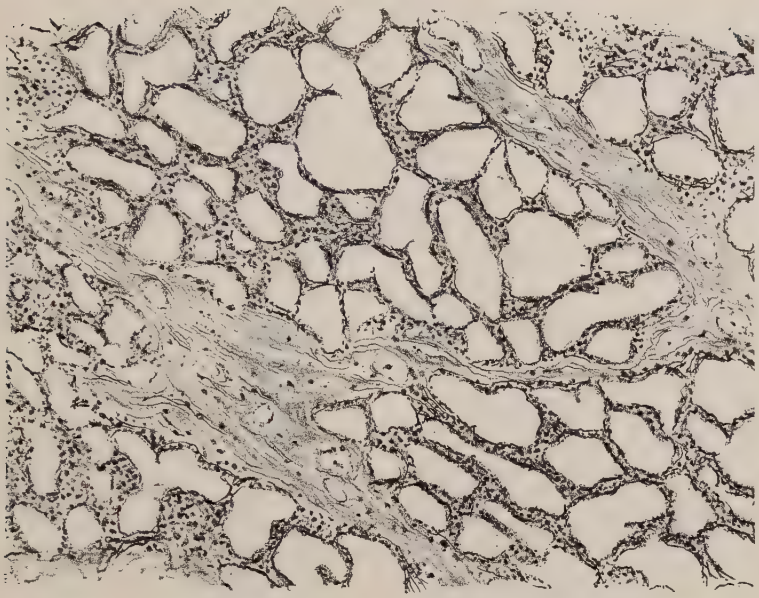


FIG. 313*C*—Full lactation hypertrophy. × 90. (*Preparation by Professor McFarland*)

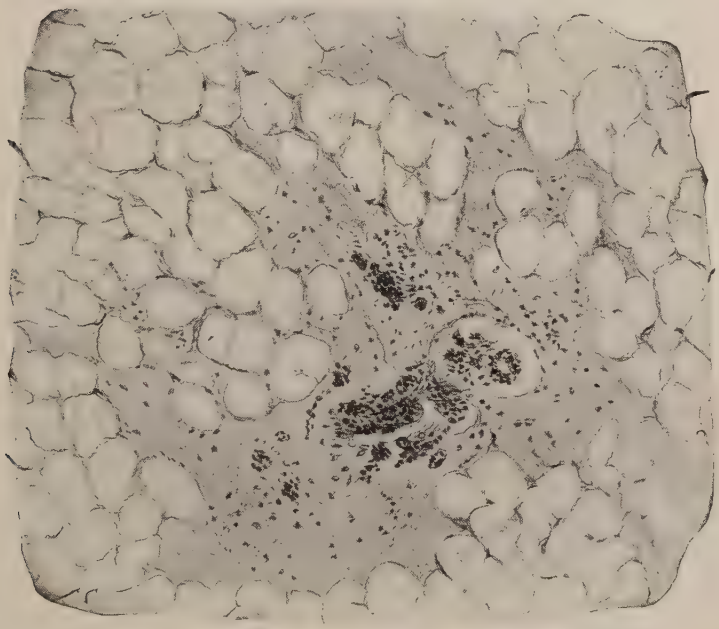


FIG. 313*D*—Complete involution. × 90. (*Preparation by Professor McFarland*)

in size, displace the nucleus towards the membrana propria and project into the lumen of the alveolus, being separated from the latter by only a thin protoplasmic envelope. With the rupture of the cells the oil drops escape into the albuminous fluid, additionally secreted by the cells, that occupy the alveolus. After liberation of the oil droplets, the epithelial cells are much reduced; after a time, however, they again become the seat of renewed secretory activity, the accumulation of fat and the production of milk. Destruction of the secreting cells, therefore, does not take place.

The **lactiferous ducts** begin as the small canals into which the alveoli open and, at first, resemble the terminal compartments of the gland, being lined with a delicate stratum of muscle, upon which rests a simple cuboidal epithelium. Within the lactiferous ducts, formed by the junction of the smaller canals, the cuboid cells are succeeded by columnar ones On ap-

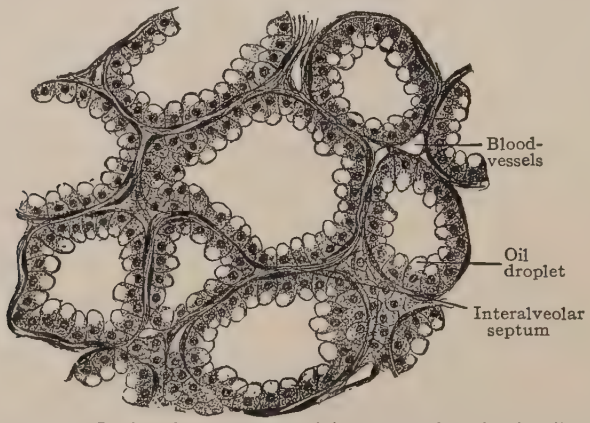


FIG. 314—Section of mammary gland during lactation, showing distended alveoli lined with secretion-bearing cells. × 170.

proaching the base of the nipple, beneath the colored areola, each milk-duct enlarges into a spindle-form **ampulla,** or **sinus lactiferus,** from 10–12 mm. long and about half as wide, that serves as a temporary reservoir for the secretion of the gland. Beyond the ampulla the duct narrows (2 mm.), passes into the nipple, and ends, after ascending the latter parallel with the other ducts, in a minute orifice (.5–.7 mm.) at the summit of the nipple. Just before terminating, the epithelium lining the duct assumes the stratified squamous character of the adjacent epidermis.

The skin covering the **areola** and **nipple,** delicate but more or less pigmented, contains well marked bundles of unstriped muscle, whose contractions cause the nipple to become prominent and erect. Within the areola, this contractile tissue forms a layer, in places almost 2 mm. thick, that encircles the base of the nipple and extends into its substance as a muscular network through which the milk-ducts pass. Deeper longitudinal strands of unstriped muscle occupy the axis of the nipple.

Over both areola and nipple the skin is provided with large **sebaceous glands,** the secretion of which is increased during lactation and serves as

protection during nursing. Sweat-glands are wanting over the nipple, but are large and modified in the periphery of the areola. The surface of the latter is modelled, especially towards the close of pregnancy, by low rounded elevations that mark the position of the subcutaneous **areolar glands** of Montgomery. The latter are rudimentary accessory masses of glandular tissue, from 1–4 mm. in diameter, and correspond in general structure with the mammary glands. Their ducts open by minute orifices on the surface of the areola.

Milk.—The fully established secretion of the mammary gland is an emulsion, the fat-globules being suspended in a clear, colorless, watery plasma. The composition of human milk includes over 88 per cent. of water, about 3 of proteins, 4 of fat, 5 of lactose, and less than 1 per cent. of salts. The chief morphological constituents of milk, are the **milk-globules,** as oil droplets liberated from the alveolar cells are called; these vary in size from the most minute spherules to those having a diameter of 3–5 μ or more. Their aver-

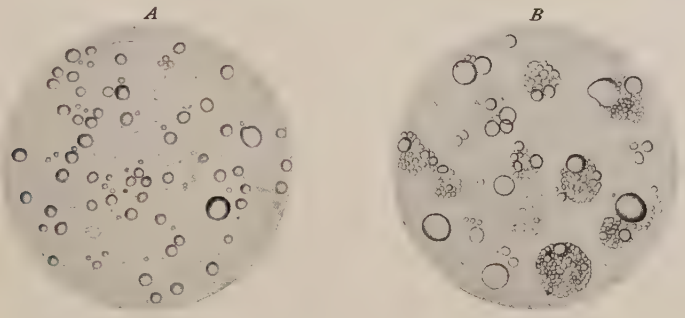


FIG. 315—Human milk *A*, ordinary secretion; *B*, showing colostrum corpuscles and oil drops. × 400.

age number per cubic millimeter is something over one million (Bouchut). The milk-globules are enclosed within extremely thin envelopes formerly believed to be constituted of casein, but recent investigations indicate that this is not true. It is probable that the fat-particles are not produced within the gland-cells, but are taken up, aggregated, and temporarily stored by their cytoplasm. A variable number of migratory leucocytes, more or less filled with fat-particles, are usually present in milk.

During the last weeks of gestation and for two or three days after its termination the breasts contain a clear secretion, known as **colostrum** milk, that differs from milk after lactation is established in possessing relatively less fat and numerous conspicuous bodies, the **colostrum corpuscles.** The latter are spherical, but may be irregular in outline, and measure from 12–18 μ, although they may attain a diameter of more than 40 μ. The corpuscles are leucocytes greatly distended with fat-particles and modified alveolar epithelial cells. Their cytoplasm is markedly granular and often of a yellowish or reddish-yellow tint. Quite commonly the mammary glands in both sexes, during the first few days after birth, yield a secretion resembling colostrum, popularly known as "witch-milk."

At birth the gland is represented by the lactiferous ducts with their ampullæ, and the smaller collecting ducts. The mammæ remain small and immature during childhood until the approach of sexual maturity, when they increase in size and rotundity. The full development of the true gland is deferred until the occurrence of pregnancy, when active proliferation and increase of the gland-tissue takes place in preparation for its activity as a milk-producing organ. After lactation has ended, the mammæ undergo involution, the glandular tissue being reduced and returning to a condition resembling that before pregnancy. With the recurrence of the latter, the gland again enters upon a period of renewed growth and preparation, to be followed in time by return to the resting condition, in which the amount of glandular tissue is inconspicuous. After cessation of menstruation, the mammary gland gradually decreases in size, and in advanced age the corpus mammæ may be reduced to a fibrous disk in which gland-tissue is almost, if indeed not entirely, wanting, only ducts remaining.

The **blood-vessels** supplying the mammary gland, in addition to their distribution to the skin and more superficial parts of the breast, send deeper twigs to the glandular tissue which breaks up into capillary networks surrounding the alveoli. During lactation the vascular supply is materially increased. The veins from the corpus mammæ join the superficial vessel and, in the main, follow the arteries. Within the areola, the subcutaneous veins form a plexus that encircles the nipple that receives its blood. The **lymphatics** are exceptionally numerous and important. The deeper ones lie within the interlobular connective tissue and pass towards the surface, where they join the rich subareolar network. With the exception of a few trunks that follow the perforating arteries and become efferents of the internal mammary lymph-nodes, the lymphatics of the breast form two or three large trunks that pass to the axillary nodes. The **nerves** supplying the glandular tissue are chiefly sympathetic fibres, some ending in the blood-vessels and others forming plexuses upon the membrana propria of the alveoli, a few fibrils terminating between the secreting cells.

RUDIMENTARY ORGANS REPRESENTING FETAL REMAINS

In the male the Wolffian body and its duct play very important rôles in the development of the excretory canal for the sexual gland, while the Müllerian duct remains rudimentary. In the female the converse is true, the Müllerian ducts form the excretory canals—the oviducts, the uterus, and the vagina—while the Wolffian structures are of secondary importance and give rise to rudimentary and functionless organs, situated chiefly in the vicinity of the ovary and the Fallopian tube between the layers of the broad ligament. These fetal remains include: the **epoöphoron, Gartner's duct,** the **paroöphoron,** and the **vesicular appendages.**

The **epoöphoron,** also called the **parovarium** or **organ of Rosenmüller,** lies between the layers of the broad ligament, in the area bounded by the ampulla of the oviduct, the ovarian fimbria, and the tubal pole of the ovary. It is flat, triangular, or trapezoidal in outline, and measures from 2–2.5 cm. in length. It consists of from eight to twenty narrow wavy tubules, the **ductuli transversi,** which, beginning with closed and slightly dilated ends, diverge from the vicinity of the hilum of the ovary and join, almost at right angles, a common chief duct that lies close and parallel to the oviduct, bearing to the smaller tubules the relation of the back of a comb to its teeth. The transverse tubules are the remains of some of the tubules of the Wolffian body; the common canal, the **ductus**

longitudinalis, is closed at both ends and represents a persistent portion of the Wolffian duct. The longitudinal duct may be interrupted and connected with the tubules in groups, or, on the other hand, it may be prolonged as Gartner's duct far beyond its usual length. In the child, the transverse tubules (.3–.4 mm. in diameter) usually possess a lumen, but later in life they may undergo partial or complete occlusion and may be the seat of cysts. The walls of the tubules and duct consist of a fibrous coat, which sometimes contains bundles of unstriped muscle lined with a single layer of epithelial cells that vary in form from low cuboid to columnar and occasionally bear cilia.

Gartner's duct results from the more or less extensive persistence of portions of the Wolffian duct that usually disappear by the end of fetal life; it is, therefore, a continuation, direct or interrupted, of the longitudinal duct of the epoöphoron. When complete as it very exceptionally is, the duct continues from the epoöphoron, along the oviduct and the side of the uterus, to the lower end of the vagina. Such extensive persistence is unusual, Gartner's duct being mostly limited to the lower part of the body and the upper

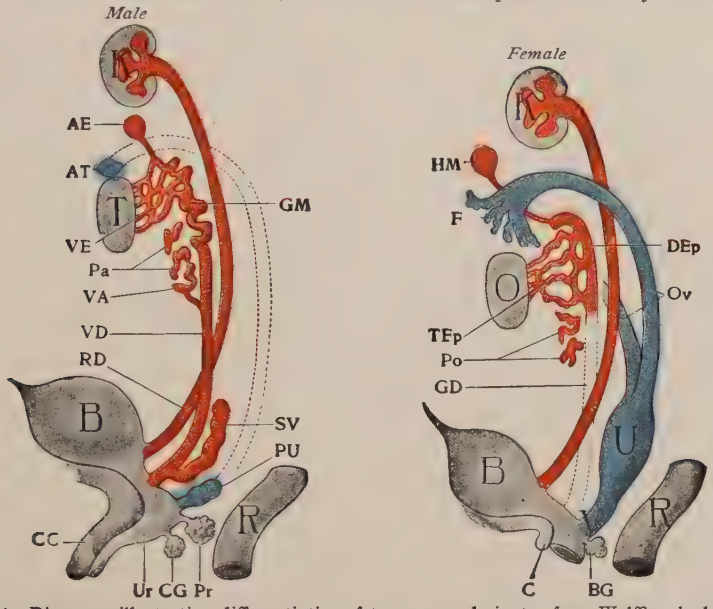


FIG. 316—Diagrams illustrating differentiation of two sexes; derivates from Wolffian body are red, those from Müllerian duct are blue. *Male:* T, testicle; VE, vasa efferentia; GM, globus major; VD, vas deferens; Pa, paradidymis; VA, vas aberrans; SV, seminal vesicle; AT, appendix testis; AE, appendix epididymidis; B, bladder; PU, prostatic utricle; Pr, prostate; Ur, urethra; CG, Cowper's gland; CC, corpus cavernosum; R, rectum; RD, renal duct; K, kidney. *Female:* O, ovary; Ov, oviduct; F, fimbria; U, uterus; V, vagina; DEp, duct of epoöphoron; TEp, tubules of epoöphoron; Po, paroöphoron; HM, hydatid of Morgagni; GD, Gartner's duct; BG, Bartholin's gland; C, clitoris; K, kidney; R, rectum. (*Modified from Wiedersheim.*)

cervix of the uterus. The canal in lined with a single layer of columnar epithelium and beset with uncertain lateral diverticula, which may be short branched tubules resembling glands. Accumulations of secretion within the duct or its diverticula may lead to the production of cysts.

The **paroöphoron** is an inconspicuous rudimentary organ distinct at birth, but usually disappearing after the second year, that lies within the broad ligament between the epoöphoron and the uterus. It consists of a small irregularly round group of blind canals, lined with a single layer of columnar epithelium, that often resemble the Wolffian tubules, which structures, in fact, they represent. A second group of similar rudimentary tubules lies lateral to the epoöphoron. It is this group, perhaps, that should be regarded as the paroöphoron proper and the homologue of the paradidymis in the male. The tubules may be the seat of cysts.

The **vesicular appendages** include the small vesicles, or hydatids, attached to the broad ligament by longer or shorter stalks. They comprise two groups, the one being represented by the conspicuous long-stalked hydatids of Morgagni and the other by the smaller vesicles, varying in form and size, connected by short stems. The **hydatid of Morgagni** is a spherical or pyriform thin-walled sac, that contains a clear fluid and usually measures from 4–8 mm. in diameter. The vesicle is attached by a slender stalk, from 1.5–4 cm. long, to the anterior surface of the broad ligament and is continuous with the upper blind end of the longitudinal duct of the epoöphoron. The hydatid consists of a fibrous coat, lined by a single layer of columnar epithelium, and covered externally by a delicate prolongation of peritoneal tissue. The **small vesicles** are attached to the anterior surface of the broad ligament, usually over the epoöphoron. The origin and morphological significance of the vesicular appendages have occasioned much discussion, but it may be accepted as established that the hydatid of Morgagni is derived from the upper end of the Wolffian duct, and is, therefore, the equivalent of the appendage of the epididymis. The smaller vesicles, which correspond in structure with the larger one, probably owe their origin to the distention and elongation of some of the transverse tubules of the epoöphoron, and, hence, are derivations of the Wolffian tubules.

THE CENTRAL NERVOUS SYSTEM

The central nervous system includes the spinal cord and the brain. These are the walls of the simple **neural tube** of the embryo, which have become greatly modified by a series of changes involving unequal growth and expansion. In contrast to the spinal segment of the neural tube, which always remains a relatively simple cylinder, the cephalic segment early differentiates into the **cerebral vesicles,** marked flexures occurring coincidently at certain points. In the sinuously bent cephalic segment are developed the various parts of the brain, while in the relatively straight spinal segment proceeds the development of the spinal cord. During the process of growth and differentiation the lumen of the original neural tube persists, giving rise to the ventricles of the brain and the minute central canal of the spinal cord.

THE SPINAL CORD

The spinal cord, or **medulla spinalis,** is that part of the central nervous system, or cerebro-spinal axis, which lies within the vertebral canal. Its form is that of a flattened cylinder, with the dorso-ventral diameter always less than the transverse one; its outline in cross-sections, therefore, is not circular, but more or less oval. Its width, moreover, is not uniform on account of two fusiform swellings, the **cervical** and **lumbar enlargements,** associated with the origin and reception of the large nerves supplying the limbs. Where least expanded, opposite the middle of the thoracic spine, the cord measures 8 mm. in its sagittal and 10 mm. in its transverse diameter. Through the cervical enlargement these respective dimensions are 9 mm. and 14 mm., and through the lumbar swelling they are 8.5 mm. and 12 mm.

Cross-sections of the spinal cord (Fig. 317), show it to be imperfectly divided into symmetrical halves by a narrow cleft, the **ventral median fissure,** in front and a partition, the **dorsal median septum,** behind. Further, the cord is seen, even with the unaided eye, to be composed of an irregular H-shaped core of gray substance enclosed by a mantle of white matter. The latter, in each half of the cord, is partially subdivided into three general tracts by the lines along which the root-fibres of the spinal nerves are attached. The **dorsal root-line** of the sensory fibres is marked by a slight furrow, the **dorso-lateral sulcus,** that lies from 2.5–3.5 mm. lateral to the dorsal median septum. The **ventral root-line,** marking the emergence of the ventral (motor) fibres, is much less evident on account of the scattered manner in which these root-fibres make their exit. In this manner three longitudinal tracts, the **white columns of the cord,** are marked off on each side—the **dorsal** between the median septum and the dorso-lateral sulcus, the **lateral** between the dorsal and ventral root-lines, and the **ventral** between the ventral root-line and median fissure. The conventional division between the ventral and lateral columns, however, is largely artificial, since neither superficially nor internally is there a definite demarcation between

these tracts. In the lower cervical and upper thoracic cord, the dorsal column is subdivided by the superficial **paramedian sulcus** and a septum of neuroglia into two wedge-shaped tracts, of which the median and smaller is the **fasciculus gracilis,** or **tract of Goll,** and the lateral and larger is the **fasciculus cuneatus,** or **tract of Burdach.**

The Gray Matter.—Within each half of the thoracic cord as seen in cross-section, the gray matter forms a linear, somewhat crescentic area, the broader end of which lies in front and the narrow one behind, with the concavity directed laterally. The convex mesial surfaces of the areas of the two sides are connected by a transverse band of gray matter, the **gray**

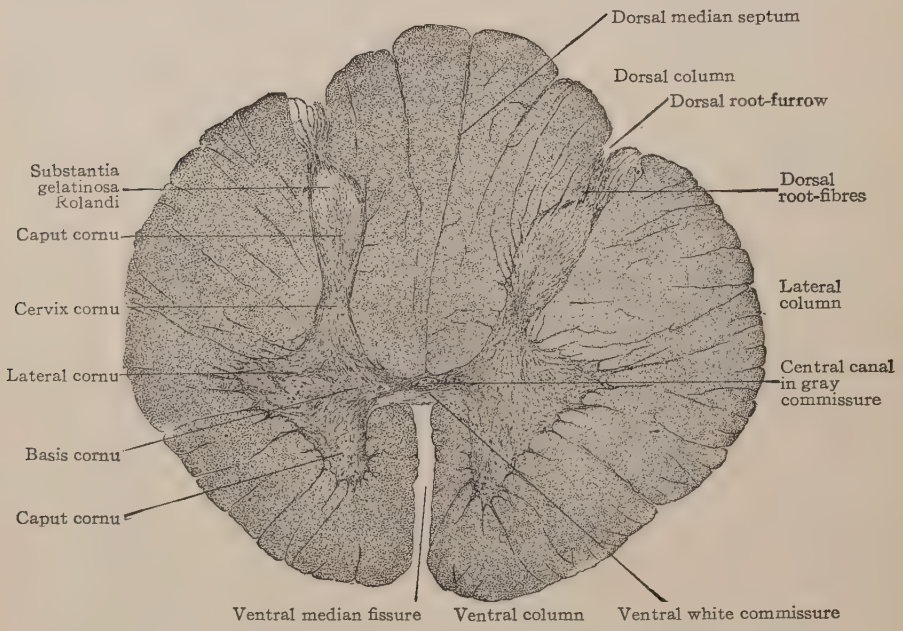


FIG. 317—Cross-section of child's cord through thoracic region, showing arrangement of gray and white matter and subdivision of the latter into columns. × 13.

commissure, that extends across the midline and encloses the minute **central canal** of the cord. The connecting band is subdivided by the canal into the **dorsal** and the **ventral gray commissure,** which lie behind and in front of the tube, respectively. The dorsal median septum reaches the dorsal surface of the gray commissure, but the ventral margin of the latter is separated from the bottom of the ventral median fissure by an intervening bridge of white matter, the **ventral white commissure,** which connects the ventral columns and provides an important pathway for fibres passing from one side of the cord to the other.

Each crescent of gray matter is divided conventionally into three parts: the **ventral** and **dorsal cornua,** the ventral and dorsal extremities of the crescent that project beyond the line of the transverse gray commissure, and the **pars intermedia,** that connects the cornua and receives the

commissure. The two horns differ markedly, but although varying greatly in details at different levels, they retain their distinctive features throughout the cord. The **ventral cornu,** or **columna grisea ventralis,** is short, thick, and rounded and separated from the surface by a considerable layer of white matter, through which the ventral root-fibres pass to their points of emergence from the cord. The blunt tip of the ventral horn is known as the **caput cornu** and the adjacent portion, by which it joins the commissure and the pars intermedia, as the **basis cornu.** The **dorsal cornu,** or **columna grisea**

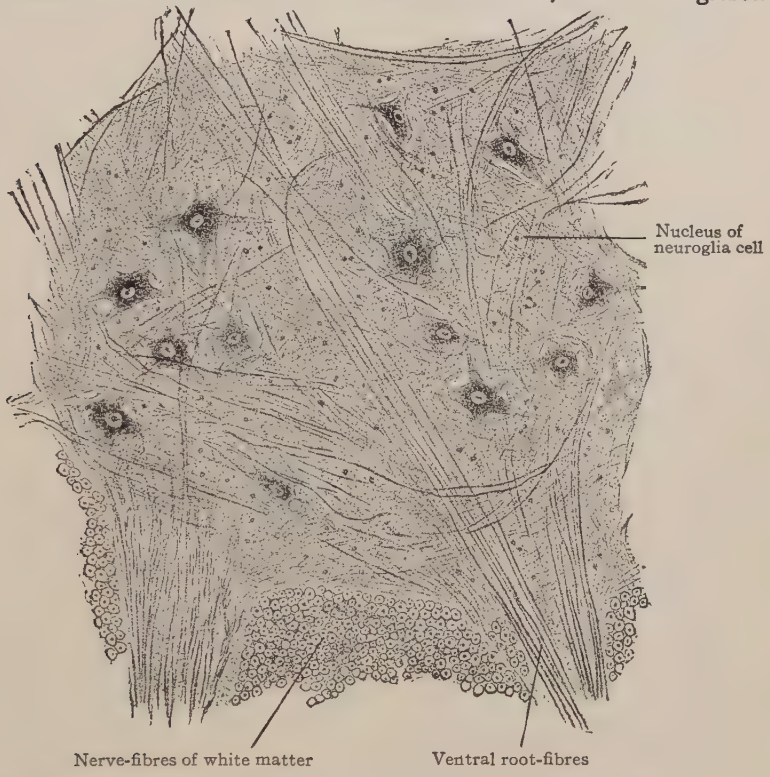


FIG. 318—Portion of ventral horn of gray matter, showing multipolar nerve-cells and root-fibres. × 120.

dorsalis, is relatively long, narrow, and pointed and extends almost to the dorso-lateral sulcus. The tip, or **apex,** of the dorsal horn is formed of a Λ–shaped stratum, the **substantia gelatinosa Rolandi,** that appears lighter and somewhat less opaque than the subjacent **caput cornu,** which it covers as a cap. The gray matter immediately surrounding the central canal has also this lighter appearance, and is termed the substantia gelatinosa centralis. Between the dorsal horn apex and the periphery of the cord, is the **marginal zone of Lissauer,** composed of fine, mostly unmyelinated, entering fibres. The greater bulk of the root-fibres, usually myelinated, enter on the medial side of this zone. The slightly contracted ventral portion of the posterior horn is the **cervix cornu.**

The fairly sharp demarcation between the gray and white matter is interrupted along the lateral border of the crescent by interminglings of gray matter with the fibres of the adjacent lateral column (Fig. 325). This is known as the **formatio reticularis** and is best developed in the upper cervical region. In the thoracic region, in addition to the dorsal and ventral cornua of gray matter there in a **lateral cornu,** or **columna lateralis.** The cells of the lateral cornu give rise to the efferent axones of the sympathetic system. These pass out with the other ventral root-fibres, but soon diverge as the white rami communicantes to reach the gangliated cord of the sympathetic.

The **histological components** of the gray matter include the nerve-cells, the nerve-fibres, and the supporting neuroglia. Of these the most distinctive elements are the multipolar nerve-cells, which lie embedded within a complex feltwork formed by the processes—dendrites, axones and

FIG. 319—Isolated root-cell from ventral horn of cord of calf; *a*, axone. × 210.

collaterals—of many neurones, by the supporting neuroglia reticulum and the blood-vessels.

The most conspicuous and important **cells of the ventral cornu** are the motor **radicular cells,** whose axones pass from the apex of the cornu, traverse the white matter (meanwhile becoming myelinated), and emerge from the cord as the axis-cylinders of the efferent (motor) root-fibres of the spinal nerves which continue directly to the voluntary striated muscles. They are multipolar, the cell-bodies appearing irregularly polygonal in cross-sections and fusiform in longitudinal ones, and measure from 65–135 μ in diameter unless unusually small, when their diameter may vary from 30–80 μ. These cells possess from three to ten dendritic processes, which radiate in various planes, divide dichotomously and finally end in terminal arborizations that may reach the dorsal horn and other parts of the gray matter. In contrast to the robust dendrites beset with spines, the axone is slender, smooth, and directly continuous with a root-fibre of a spinal nerve. With the exception

of delicate collaterals, which may be wanting, the axone is unbranched. Each nerve-cell possesses a spherical or ellipsoidal nucleus (10–20 μ), enclosed by a distinct nuclear membrane, and usually a single nucleolus, exceptionally more than one. In addition to accumulations of deeply-staining tigroid substance, the cytoplasm contains brownish-yellow pigment granules, often in the vicinity of the implantation cone from which the axone comes.

The nerve-cells of the ventral cornu are not uniformly distributed through the gray matter, but are collected into more or less definite groups that recur in consecutive sec-

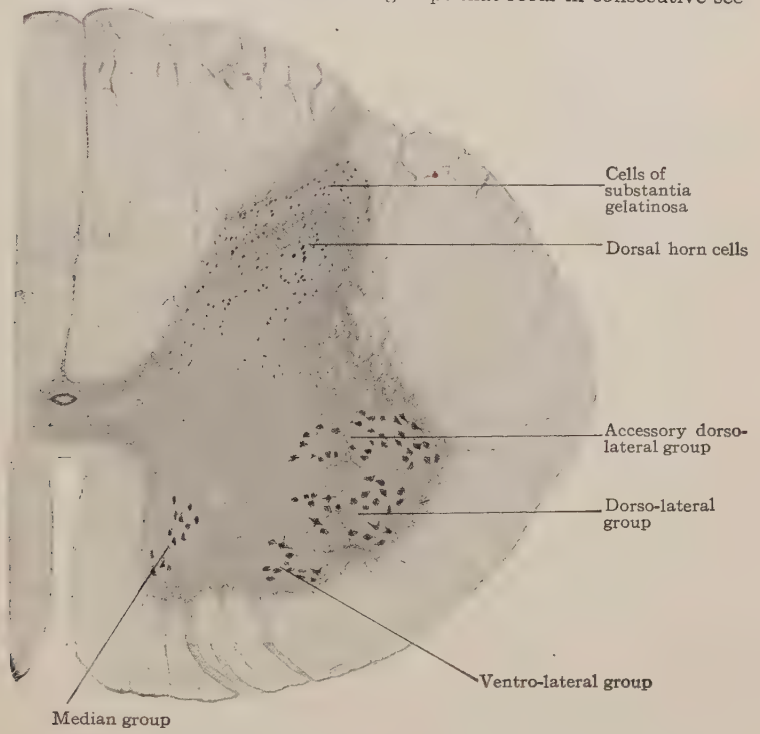


FIG. 320—Half-section of lower cervical cord, showing grouping of the nerve-cells. × 20.

tions. It is evident, therefore, that the cell-groups are not limited to a single plane, but are continuous as cell-columns for longer or shorter stretches within the gray matter. The **grouping of the nerve-cells** of the ventral cornu corresponds in a considerable degree to differences of distribution of their axones. There are two main collections, a **mesial group,** from which run the axones to the trunk musculature, and a **lateral group** from which originate the axones to the limb muscles. The mesial group extends practically throughout the entire cord, but the lateral group is not present in most of the thoracic cord nor below the third sacral nerve. These collections thus vary in extent and definition in different parts of the cord, and, where well marked, are often subdivided. This is particularly true of the lateral collection, in which a ventral and a dorsal subdivision are recognized as the **ventro-lateral** and the **dorso-lateral group** (Fig. 320). The mesial collection, situated within the ventral angle of the horn, is sometimes, but much less clearly, divisible into a **ventro-mesial** and a **dorso-mesial group,** the latter being variable and at many levels wanting.

The **nerve-cells of the dorsal cornu** are neither as large nor as regularly disposed as the ventral horn cells. Only in one locality, along the median border of the base of the dorsal cornu, are they collected into a distinct group—the cell-column of Clarke; elsewhere, they are scattered without order throughout the gray matter of the dorsal horn. In a general way, however, they may be divided into: (1) the **cells of Clarke's column,** (2) the **cells of the substantia gelatinosa Rolandi,** and (3) the **inner cells of the caput cornu.**

The **cells of Clarke's column** form a conspicuous collection that occupies the mesial border of the base of the posterior horn (Fig. 321), and correspond to an elevation on the surface of the gray matter. The cells are about 50 μ in diameter, spheroidal

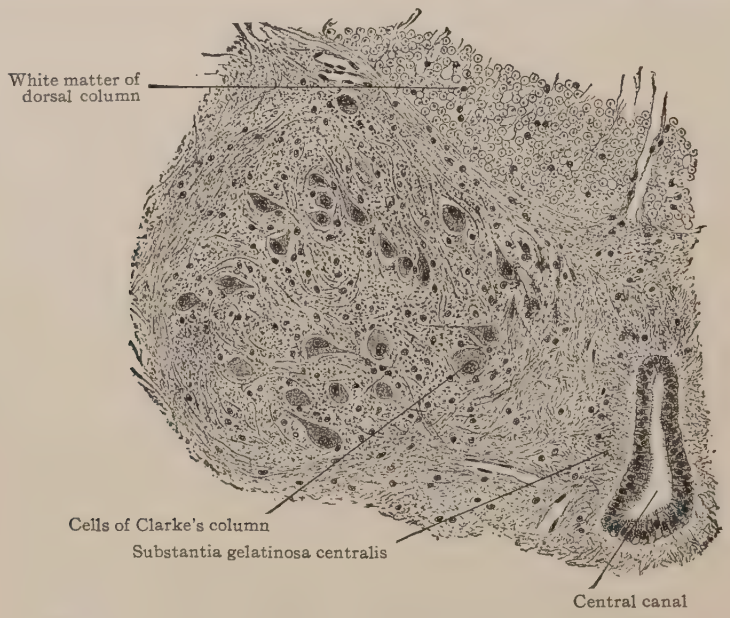


FIG. 321—Part of cord, showing cells of Clarke's column in base of dorsal horn. × 110.

in outline and possess many richly branched dendrites that radiate chiefly within the limits of the group. The axones run outward to the periphery of the lateral column within which, as the constituent fibres of the direct cerebellar tract (fasciculus spino-cerebellaris dorsalis), they turn brainwards.

The **nerve-cells of the substantia gelatinosa** are numerous, small, stellate elements, less frequently fusiform or pear-shaped, that measure only from 6–20 μ, although exceptionally larger. Their numerous short dendrites are irregularly disposed and branched. The axones are continued partly into the white matter of the lateral column, where they divide into ascending and descending limbs, and partly into the adjacent gray matter. Around these cells probably terminate the unmyelinated fibres of the entering dorsal root which thus form part of the pathway for protopathic impulses from the body (pain, temperature). These are relayed to the brain through the ventral spino-thalamic tracts. The **marginal cells** are fusiform or pyramidal and larger (35–55 μ) and occupy the outer border of the substantia gelatinosa. Their axones traverse the substantia gelatinosa and probably continue, for the most part, within the lateral column both of the same and of the opposite side. Many of the nerve-cells within the substantia gelatinosa were formerly

regarded as glia cells; instead of such being the case, this region of the gray matter is relatively poor in neuroglia and numerically rich in nerve-cells.

The **inner cells** of the dorsal cornu, intermingled with numerous nervous elements of small size, are triangular or spindle-shaped and usually measure about 50 μ; they are, therefore, larger than the ordinary cells of the substantia gelatinosa. Their axones pass mostly into the lateral column of the same side; some, however, have been traced into the opposite side. A few cells of type II—those whose axones are not prolonged into nerve-fibres but soon break up into elaborate end-arborizations confined to the gray matter—are found within the gray matter of the dorsal cornua.

The **nerve-cells of the pars intermedia,** the gray matter which connects the horns and lies opposite the gray commissure, may be divided broadly into two classes, the **lateral** and the **middle cells,** that occupy respectively the outer border and the more central area of this part of the gray matter. Those of the first class, or **intermedio-lateral cells,** are associated with the lateral horn and adjacent gray matter and, hence, are also called the **group,** or **column, of the lateral horn.** This extends throughout the entire thoracic and the upper two or three segments of the lumbar cord. The cells are multipolar or fusiform, from 15–45 μ in diameter, and provided with a variable number of dendrites. The axones pass out with the ventral roots, but soon leave these to form the white rami communicantes to the sympathetic ganglia of the gangliated cord. These axones are known as pre-ganglionic fibres of the sympathetic system. The cells of the second class, the **intermediate cells,** are irregularly disposed and only in the upper part of the cord present a fairly distinct middle group. They are polygonal or fusiform, small in size, and provided with irregular dendrites. Their connections are not definitely known.

A few isolated nerve-cells are usually to be found within the white matter in the vicinity of the more superficially placed cell-columns. These, the so-called **outlying cells,** are regarded as elements displaced from their usual position during the differentiation and growth of the white and gray matter. Similar displacement sometimes affects the cells of the spinal ganglia, which then may be found within the cord.

The **neuroglia of the gray matter** is everywhere present as a delicate reticulum supporting the nerve-cells and fibres. The structure of neuroglia having already been described, the special features of its arrangement may be noted. The feltwork of neuroglia fibrils within the gray matter is, in general, more compact than within the white matter and, further, somewhat denser at the periphery than in the deeper parts of the gray core. There is, however, no sharp boundary between the supporting tissue of the white and gray tracts, since numerous glia fibrils extend outwards from the framework of the gray substance to be lost between the nerve fibres of the adjoining columns. This feature is marked in the ventral cornu, where the glia fibrils form septa of considerable thickness that diverge into the surrounding white columns; moreover, the conspicuous processes of the formatio reticularis and the projecting lateral horn consist largely of neuroglia. The larger nerve-cells and their more robust processes are ensheathed by interlacements of neuroglia fibrillæ. The amount of neuroglia varies in the several parts of the dorsal horn; thus, the extreme apex consists almost entirely of glia tissue, although within the substantia gelatinosa Rolandi the number of glia fibres is unusually meagre. Within the caput and remaining parts of the dorsal horn, the neuroglia elements are similar in quantity and disposition to those in the ventral cornu.

Substantia gelatinosa centralis is the name given to a zone of peculiar translucency that immediately surrounds the central canal. This annular area consists of modified neuroglia in which radial ependymal fibres, continued from the ependymal cells lining the central canal, are interwoven

with circularly disposed neuroglia fibrillæ, the whole being a compact stratum interspersed with an unusual number of glia cells. In marked contrast to the substantia gelatinosa which caps the posterior horns, that surrounding the central canal contains few nerve-cells and chiefly glia elements.

The **nerve-fibres of the gray matter** constitute a considerable part of the intricate groundwork in which the nerve-cells are embedded. The fibres seen traversing the gray matter in all directions are the processes contributed by neurones situated at the same, different, or even remote levels, and include: (1) the collaterals and terminal stems of the dorsal root-fibres that enter the gray matter; (2) terminal fibres of the descending tracts that end in relation with the ventral (motor) radicular cells; (3) the axones and collaterals from the numerous cells of the dorsal horn that traverse the gray matter to and from the respective columns in which they course. The dendritic processes also contribute to the complex.

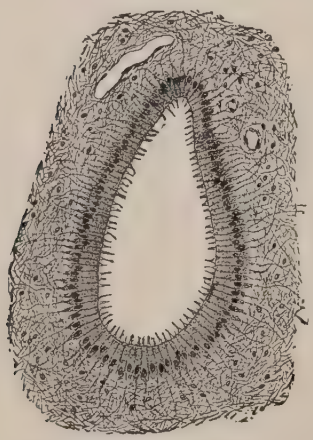


Fig. 322—Central canal and surrounding substantia gelatinosa centralis from child's cord; the canal is lined with ependymal cells, outside which lies the neuroglia. × 135.

The White Matter.—Since the predominating components of the white substance are longitudinal nerve-fibres that pass for a longer or shorter distance up and down in the columns of the cord, in transverse sections the field between the gray core and the surface is made up chiefly by the cross-sections of the myelinated nerve-fibres. These appear as small, closely set rings (Fig. 323), enclosing deeply-stained dots, surrounded by faint annular striations. The dots are sections of the axis-cylinders, the annular striations the remains of the framework of the myelin sheath, and the rings the slight condensations of the neuroglia that take the place of a neurilemma, which is absent on the fibres of the cerebro-spinal axis. The individual nerve-fibres vary greatly in size, even within the same tract large and small ones often lying side by side. The smallest may be less than 5 μ in diameter and the largest over 25 μ.

The immediate surface of the white matter, beneath the investing pia mater, is formed by a tract of condensed **neuroglia,** the **subpial layer,** that is devoid of nervous elements and constitutes the definite outer boundary of the cord. This zone consists of a dense interlacement of circular, longitudinal, and radial neuroglia fibrils, along with many glia cells. From the deeper surface of this investment numerous bundles of fibrillæ penetrate between the nerve-fibres and become lost in the general supporting groundwork. At certain points the bundles are reinforced by robust septa which imperfectly separate the nerve-fibres into groups or tracts, as conspicuously seen in the paramedian septum subdividing the dorsal column. The blood-vessels that enter the nervous substance of the cord from the pia mater, accompanied by connective tissue, are surrounded by tubular sheaths of neuroglia. These develop in the following manner. In the embryo when the

spinal cord is being vascularized, the blood-vessels push in before them the external limiting membrane (membrana limitans gliosa). The blood-vessels do not actually come into direct contact with the nerve-cells, for always there is this glial membrane interposed. The spaces often seen between the capillaries and the membrane are the **Virchow-Robin spaces.**

The Fibre Tracts.—Although microscopical examination of ordinary sections of the cord affords slight indication of a subdivision of the columns of white matter into areas corresponding with definite fibre-tracts, yet the

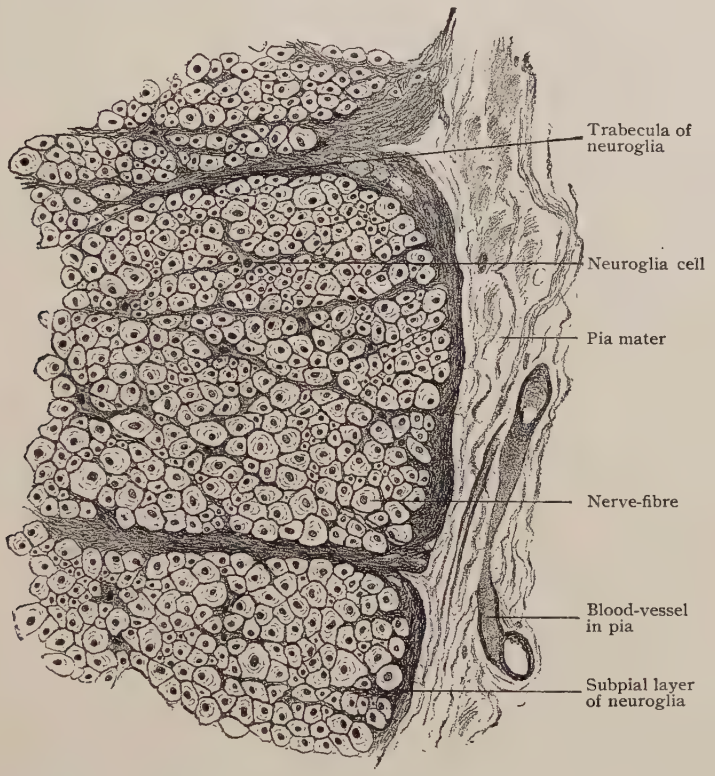


FIG. 323—Part of periphery of cord, showing subdivision of white matter by ingrowths of subpial layer of neuroglia. × 230.

combined evidence contributed by anatomical, pathological, embryological, and experimental investigation establishes the existence of a number of such paths of conduction. With few exceptions however, they are without sharp boundaries, adjoining tracts often overlapping. In addition to being provided with paths of conduction necessary for the performance of its function as a centre for independent, or reflex, impulses in response to external stimuli, the cord contains tracts that connect it with the brain, as well as those that bring the various levels of the cord itself into association. The white matter contains, therefore, three classes of nerve-fibres: (1) those entering the cord from the periphery and other parts of the body; (2) those

entering it from the brain; and (3) those arising from the nerve-cells situated within the cord itself. It is evident that some of these fibres constitute pathways for the transmission of impulses from lower to higher levels and hence form **ascending tracts,** while others, which conduct impulses in the opposite direction, form **descending tracts.**

The accompanying schematic figure (Fig. 324) shows the general relations of the most important paths of the cord, but is not to be regarded as accurately representing the actual form and size of the fibre-tracts. For it must be appreciated that the definite limits of these tracts in such diagrammatic representation seldom exist in reality, since the fibres of the adjacent paths in most cases overlap, or, indeed, extensively intermingle, so that the fields marked in cross-sections may be shared by fibres belonging to different

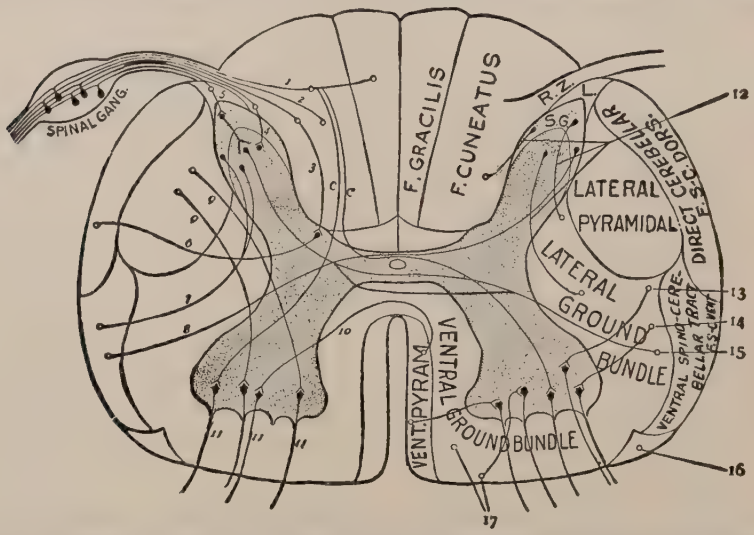


FIG. 324—Diagram of spinal cord, showing position of chief tracts and relations of their component fibres to nerve-cells; 1–5, dorsal root-fibres entering root-zone (R.Z.) and Lissauer's tract (L.), open circles (o) indicate that fibres pass up and down; *c, c,* collaterals from long ascending tracts (1, 2) to ventral root-cells; 3, fibres ending around cells of Clarke's column; 6, fibres forming direct cerebellar tract; 7, 8, fibres forming ventral spino-cerebellar tract (F.S.–C.V.); 9, 10, fibres from lateral and ventral pyramidal tract; 11, 11, 11, ventral root-fibres; 12, association tracts; 13, rubro-spinal; 14, tecto-spinal lateral; 15, spino-thalamic lateral; 16, olivo-spinal and spino-olivary tracts; 17, vestibulo-spinal.

systems. Also the number of fibres in any tract changes as it proceeds through the cord.

The constitution of the fibre-tracts of the cerebro-spinal axis is manifestly beyond the province of these pages. For such information the reader is referred to the systematic text-books of anatomy and the special works on the nervous system. A few considerations of importance, however, may here find appropriate mention.

All afferent, or sensory, impulses entering the cord do so by way of the dorsal root-fibres. The latter are the centrally directed processes (axones) of the neurones whose cell-bodies are the ganglion-cells within the spinal ganglia situated on the dorsal roots of the spinal nerves. These root-fibres convey to the cord the various impulses collected by the peripherally

directed processes (the sensory nerves) from the integument, mucous membranes, muscles, tendons, and joints, from all parts of the body with the exception of those served by the cranial nerves. Some of the afferent impulses thus conducted are transformed in the cerebrum into impressions of touch, pressure-sense, and temperature, while others are carried to the cerebellum, which responds by muscular impulses necessary to maintain coördination.

Fig. 325—Section of spinal cord at level of second cervical segment; formatio reticularis fills bay between dorsal and ventral cornua; substantia gelatinosa caps apex of dorsal cornu. (*Drawn from Weigert-Pal preparation made by Professor Spiller.*) × 6.

On entering the spinal cord along the dorso-lateral sulcus, most of the dorsal root-fibres penetrate the fasciculus cuneatus (tract of Burdach) and, with few exceptions, undergo a ≻ or ⊢ like branching into ascending and descending limbs which assume a longitudinal course and pass up and down in the cord for a variable distance. During their course both limbs give off collateral branches which bend sharply inward and pass horizontally into the gray matter to end chiefly in relation with the cells of the dorsal

Fig. 326—Section of cord through lower part of cervical region. × 6. (*Preparation by Professor Spiller.*)

horns, from which cells new secondary paths arise. The main stem-fibres of the descending and of the short ascending limbs also end in the manner just described. In addition to the short collaterals destined for the

cells of the dorsal horn, others, the **ventral reflex collaterals,** traverse the dorsal horn and intermediate gray matter to end in arborizations around the ventral radicular cells, and thus complete important reflex arcs by which impulses transmitted through the dorsal roots directly impress the motor neurones. With the possible exception of certain fibres said to pass directly to the cerebellum, all the sensory root-fibres end around neurones situated either within the gray matter of the spinal cord or within the nuclei of the medulla. Thence the impressions are conveyed by axones of these secondary neurones to higher centres, to be taken up in turn by tertiary neurones, in the sequence of the chain required to complete the path for the conduction and distribution of the impulse.

The long **ascending dorsal tract** includes the dorsal root-fibres that pass uninterruptedly upwards within the dorsal column (within the tracts of Goll and of Burdach) as far as the nuclei (gracilis and cuneatus) of the medulla. Many other root-fibres, however, ascend for only a short distance and then bend inwards to end around the cells of the dorsal horn. Among the most important of such fibres are those that pass to the neurones of Clarke's column, around which they end in telodendria. The axones of these neurones continue the path for the impulses received from the dorsal root-fibres by cutting across the gray matter and lateral column to the periphery where, bending brainwards, they form the important **dorsal spino-cerebellar,** or **direct cerebellar, tract** (*fasciculus spino-cerebellaris dorsalis*).

FIG. 327—Section of cord through middle of thoracic region. × 6. (*Preparation by Professor Spiller.*)

Among the many neurones of the dorsal horn around which the dorsal root-fibres end, some send their axones into the lateral columns to form the **ventral spino-cerebellar tract** (*fasciculus spino-cerebellaris ventralis*) which occupies the periphery of the cord immediately in advance of the dorsal spino-cerebellar tract. Others send their axones into the ventro-lateral column of the opposite side and ascend as the **spino-thalamic tracts,** sensory pathways of importance for protopathic stimuli.

The foregoing tracts are all concerned in transmitting, directly or indirectly, the impulses brought by the dorsal root-fibres to higher levels; they are all, therefore, ascending paths. In order, however, that the spinal cord with its long series of motor nerves shall be brought under the influence of the volitional and coördinating impulses arising within the cerebrum and cerebellum, respectively, it is evident that descending tracts composed of efferent fibres exist. Such fibres, connecting the motor cells of the cerebral cortex with the motor root-cells of the spinal nerves, are condensed into two chief strands, the **ventral** and **lateral pyramidal tracts.** The latter (*fasciculus cerebro-spinalis lateralis* or *fasciculus cortico-spinalis lateralis*) occupies

an oval area between the lateral aspect of the dorsal horn and the direct cerebellar tract. The component fibres are the axones of the motor cortical neurones, which have descended from the white core of the cerebrum, through the ventral part of the brain-stem (cerebral peduncle, pons, and medulla), to the lower part of the medulla and thence, after crossing in the **pyramidal decussation,** into the lateral column of the cord. On reaching the level corresponding to the cord-segment to be influenced, the cerebro-spinal fibres bend inwards, enter the gray matter, and end around the motor root-cells in arborizations. The fibres of the **ventral,** or **direct, pyramidal tract** (*fasciculus cerebro-spinalis ventralis*) correspond in origin and course with those of the lateral tract until they reach the lower part of the medulla, where, instead of crossing in the pyramidal decussation, they continue into the ventral column and descend within a narrow zone along the ventral median fissure of the cord. Although not sharing the decussation in the medulla, practically all of these fibres cross somewhere in the spinal cord by way of the ventral white commissure, and pass at the appropriate level into the ventral cornu of the opposite side, to end in arborizations around the radicular cells. In no case does a motor impulse pass directly from the cerebral cortex to the muscle fibre, since always at least two links—the cortical and the spinal neurone—are required to complete the chain.

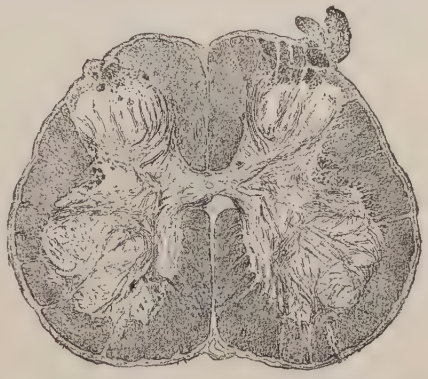


Fig. 328—Section of cord through lower part of lumbar region. × 6. (*Preparation by Professor Spiller.*)

The existence of direct paths from the cerebellar cells to those of the spinal cord is unlikely, the impulses from the cerebellum being usually carried by the axones of the cerebellar neurones to cells within the brain-stem (red, vestibular, and olivary nuclei) and thence by secondary axones (rubro-, vestibulo-, and olivo-spinal fibres) through the ventro-lateral columns to the gray matter of the cord.

Although the tracts above described include the more definite and evident of the paths of conduction, a glance at Fig. 324 shows that a considerable part of the ventral and lateral columns of the cord is still unaccounted for. To this extensive area the name **ventro-lateral ground-bundle** is conveniently applied; within its complex are many fibres which serve as links binding together different levels of the cord itself. These **intersegmental association fibres,** are for the most part short, passing as the axones of the dorsal horn cells into the adjacent white matter and, after a limited course, bending inwards to enter the gray matter once more and to end around the nerve-cells at some different level. The shorter association tracts lie close to the gray matter, while the longer ones run within the more peripheral part of the ventro-lateral ground-bundle.

The **blood-vessels** supplying the spinal cord, derived from many sources, form an arterial network within the pia mater that accompanies the nervous cylinder throughout its length. The gray matter receives its principal supply from the series of **ventral fissural arteries,** over two hunded in number, that pass from the ventral spinal trunk backwards within the ventral median fissure to its bottom and there divide into right and left branches, which traverse the ventral white commissure to gain the gray matter on either side of the central canal. These vessels, the **sulco-marginal arteries,** divide into ascending and descending branches that provide a rich capillary network for the entire gray matter, with the exception of its most peripheral zone. The latter, together with the white matter, receives its supply from the **penetrating arterioles** that come from the surrounding intrapial trunks and enter the subjacent surface of the cord. Unpaired horizontal twigs, the **dorsal sulcal arteries,** follow the dorsal median septum at different levels for some distance, but before reaching the dorsal gray commissure usually break up into terminal ramifications, some of which pass to the gray matter of the dorsal horns. Notwithstanding the capillary anastomoses within the nervous tissue, each artery provides the sole available supply for some definite territory; they are, therefore, "end-arteries," a fact which explains the extensive and elaborate system of vessels necessary to maintain the nutrition of the cord. The plexiform veins within the spinal pia are formed by the union of the small radicles that collect the blood from the intraspinal capillaries and emerge at the surface of the cord. Definite lymphatics within the spinal cord are unknown.

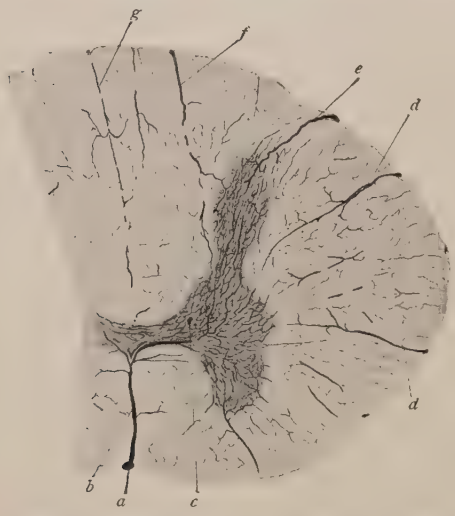


FIG. 329—Transverse section of injected cord, showing vascular supply of white and gray matter; *a*, anterior spinal giving off anterior sulcal (*b*); *c*, ascending branch; *d*, perforating arteries; *e*, postero-lateral, *f*, parasulcal; *g*, posterior sulcal. × 10.

The **investing membranes,** or **meninges,** of the spinal cord are described in connection with those of the brain.

THE BRAIN

A brief survey of the gross anatomy of the human brain, or **encephalon,** is an advantageous introduction to the study of its internal structure. The largest part of the human brain is composed of the cerebral hemispheres, and by inspection are seen their conventional subdivisions into frontal, parietal, occipital, and temporal lobes.

When the brain, denuded of its investing membranes, is viewed from

below (Fig. 330), there is seen the median **brain-stem,** that inferiorly is directly continuous with the spinal cord, through the foramen magnum, and above divides into two diverging arms that disappear within the large overhanging mass of the cerebrum. The brain-stem in this view shows three divisions, the inferior of which, the **medulla oblongata,** is the upward prolongation of the spinal cord and above is limited by the lower border of the quadrilateral mass of the next division, the **pons Varolii.** Beyond the upper margin of the pons, the brain-stem is represented by a third division that ventrally is separated by a deep recess into two diverging limbs, the **cerebral**

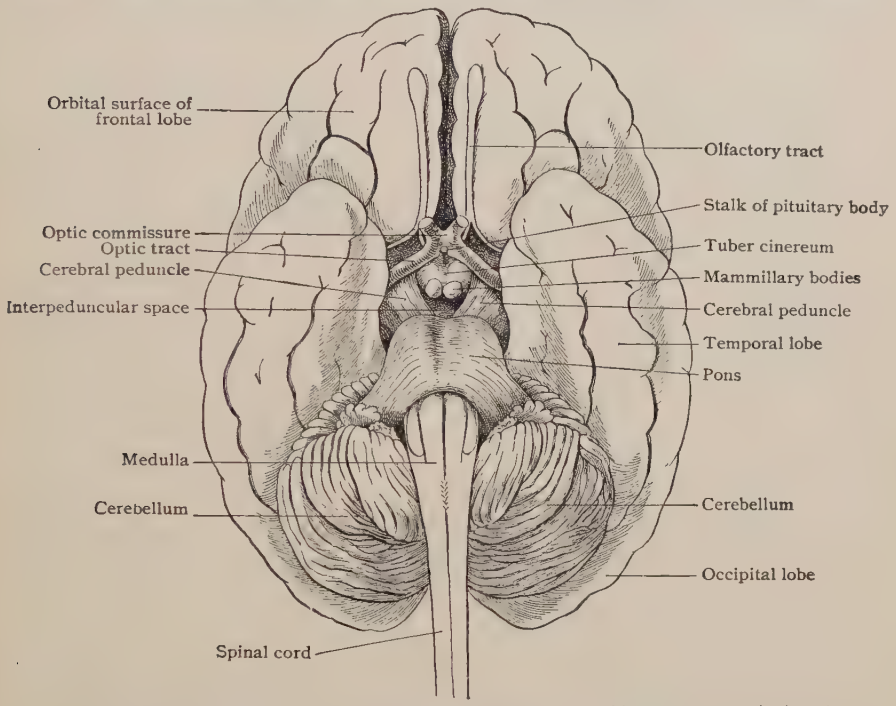


FIG. 330—Human brain, viewed from below, showing relations of brain-stem to spinal cord and cerebrum, as well as more prominent details of brain.

peduncles, or **crura cerebri,** which are the ventral portions of the mid-brain. Each of the peduncles then continues into the homolateral half of the cerebrum, and thus connects the cerebrum with the lower levels of the cerebrospinal axis. The greater part of the medulla and pons is seen to be covered dorsally by the **cerebellum,** whose large lateral expansions, or **hemispheres,** project on either side as conspicuous masses distinguished by the closely set plications and intervening fissures that mark their surface. Both the cerebral hemispheres and the cerebellum are coated with cortical gray matter, in which, broadly speaking, are situated the neurones that constitute the end-stations for the sensory impulses conveyed by the various corticopetal paths and the centres controlling the lower-lying nuclei of the motor nerves. The brain-stem on the other hand, whilst containing numerous stations for

the reception and distribution of impulses through the attached cranial nerves, is also the great pathway by which the cerebrum and the cerebellum are connected with each other and with the spinal cord.

Viewed in a mesial sagittal section (Fig. 331), each division of the brain is seen to contain some part of the system of communicating spaces that as the **lateral** and **third ventricles,** the **aqueduct of Sylvius,** and the **fourth ventricle,** extend from the cerebral hemispheres above through the brain-stem and beneath the cerebellum to the **central canal** of the spinal cord below. Both the roof and the floor of the irregular **third ventricle** are thin, while its lateral walls are formed by two robust masses, the **optic thalami.** The thin **roof** of the ventricle consists of the delicate layer of **ependyma,** as

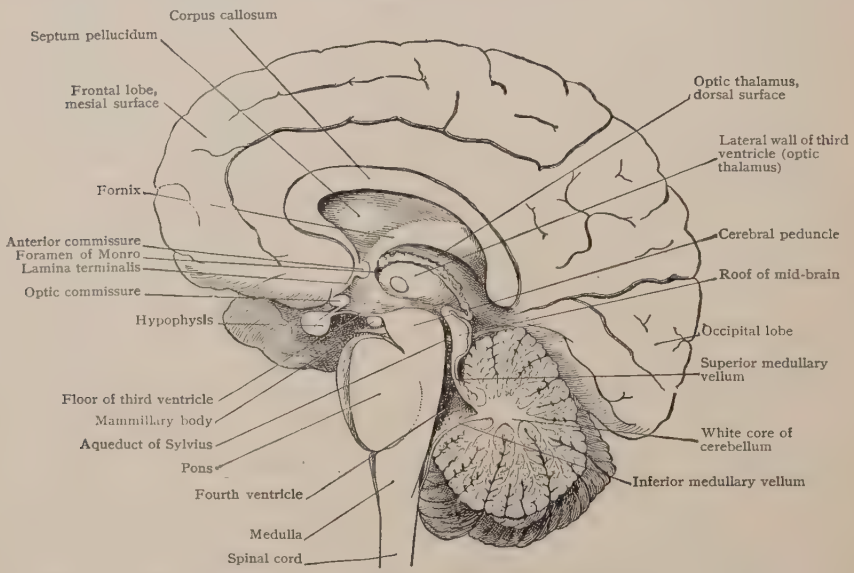


FIG. 331—Human brain seen in mesial sagittal section, showing relations of brain-stem, cerebrum and cerebellum, and the ventricles.

the immediate lining of the ventricular spaces is designated, and on this rests a closely adherent fold of pia mater. The two structures, the ependyma and the pia mater, together constitute the membranous **velum interpositum** that forms the roof of the ventricle. During embryonic development the blood-vessels of the pia invaginate the thin ependymal layer so that little tufts of capillaries project into the ventricle, constituting the **choroid plexus of the third ventricle.** From the lateral borders of the velum interpositum, blood-vessels invaginate the adjacent thin mesial walls of the cerebral hemispheres, beginning anteriorly near the foramina of Monro. These vascular intrusions form the **choroid plexuses of the lateral ventricles.** At the posterior end of the roof of the third ventricle, is attached the cone-shaped **pineal body.** The floor of the third ventricle is also, for the most part, thin and irregular. It corresponds to the median part of the lozenge-shaped area, the **interpeduncular space,** bounded behind by the diverging

cerebral peduncles and in front by the **optic chiasm** and **optic tracts.** Here are seen the paired **corpora mamillaria,** the **tuber cinereum,** and the stalk of the **pituitary body.**

The **Sylvian aqueduct,** or **iter,** the narrow canal traversing the mid-brain, connects the third and fourth ventricles. Above it lies the quadrigeminal plate, whose free dorsal surface is modelled by two pairs of rounded elevations the **corpora quadrigemina.** The **fourth ventricle** in sagittal section appears as a triangular space, the anterior, or basal, wall being the dorsal surface of the pons and medulla and the posteriorly directed apex lying beneath the cerebellum. When the cerebellum is removed and the ventricle viewed from behind, the ventricle is seen to be rhomboidal in outline, the lateral boundaries above being the **superior cerebellar peduncles,** that converge as they ascend from the cerebellum to the sides of the corpora quadrigemina; similar arms, the **inferior cerebellar peduncles,** also known as the **restiform bodies,** ascend divergingly from the lateral columns of the medulla and form the lower lateral boundaries of the fourth ventricle. Along the floor of the fourth ventricle, and of the Sylvian aqueduct lies an important sheath of gray matter, continuous with that surrounding the central canal of the spinal cord. Within the white matter of each cerebral hemisphere are embedded two large gray masses, the **corpus striatum** and the **optic thalamus,** often together termed the **basal ganglia.** The optic thalamus is of especial importance as the station towards which, in a general way, all afferent (sensory) impulses destined for the brain converge.

THE MEDULLA OBLONGATA

The medulla oblongata, or **bulb,** is the lowest segment of the brain-stem and the direct upward prolongation of the spinal cord. It is regarded as beginning below at the lower border of the foramen magnum and extends upwards to the lower margin of the pons, a distance of about 2.5 cm. Its general form is tapering, increasing in breadth from that of the cervical cord (10 mm.) below, to about twice as much (18 mm.) above, and in the dorso-ventral dimension from 8 to 15 mm.

In many respects the medulla appears to be the direct continuation of the spinal cord. This correspondence, however, is only partial, cross-sections of the medulla revealing the presence of considerable masses of gray matter and important tracts of nerve-fibres not represented in the cord, as well as the rearrangement, modification or disappearance of spinal components prolonged into the bulb.

Each half of the medulla is subdivided into three longitudinal areas, **ventral, lateral,** and **dorsal,** by two grooves situated at some distance from the midline. Of these, the **ventro-lateral furrow** marks the emergence of the root-fibres of the hypoglossal nerve, which are entirely motor and correspond to the ventral roots of the spinal nerves, with which they are in series. The other groove, the **dorso-lateral furrow,** marks the attachment of the fibres of the ninth, tenth, and bulbar part of the eleventh cranial nerves. These fibres are both afferent and efferent and correspond only in part to the dorsal roots of the spinal nerves.

Seen in transverse sections, the medulla, even at its lower end, presents new features, and towards its upper limit varies so greatly from the cord that only slight resemblance to the latter is retained. The characteristic features displayed by sections of the medulla at different levels depend upon the changes induced chiefly by four factors: (1) the decussation of the cortico-spinal, or pyramidal, tracts, (2) the appearance of the dorsal nuclei, (3) the production of the formatio reticularis, and (4) the opening out of the fourth ventricle.

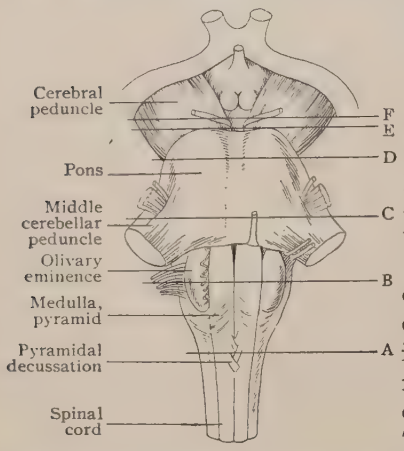


FIG. 332—Ventral aspect of brain-stem; the lines lettered on right side indicate the levels of succeeding cross-sections.

The **decussation of the cortico-spinal or pyramidal, tracts,** may usually be detected grossly, and is readily followed in consecutive sections. This tract originates in the motor cortex (precentral convolution) of the cerebral hemisphere. The fibres pass successively through the internal capsule, cerebral peduncle, base of pons, pyramid of medulla, here mostly crossing over, and continue into the lateral white column of the spinal cord, finally to end around motor radicular cells. From the latter, axones run in the peripheral nerves to reach the voluntary muscles. These two sets of neurones, an upper and a lower, are

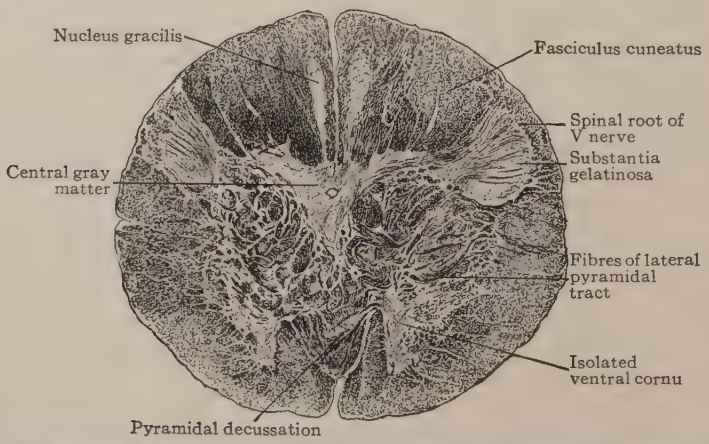


FIG. 333—Section across medulla at level A, Fig. 332; fibres of pyramidal decussation almost fill ventral median fissure; dorsal horns are displaced laterally by increased dorsal columns. × 5½. (*Preparation by Professor Spiller.*)

traversed by a stimulus passing from the brain to the muscles, resulting in a voluntary movement. Above the crossing-over, the pyramidal tract occupies the ventrally-placed pyramid on each side of the midline. Below the decussation the tract lies in the lateral white matter. In the area of

decussation, (Fig. 333), the bundles of fibres from the two tracts are seen intermingled in the midline; large strands of obliquely sectioned fibres press aside or obliterate the ventral median fissure; other bundles passing laterally separate the ventral horns of gray matter from the central gray matter. In this great motor decussation 80–90 per cent. of the pyramidal fibres cross, the remainder continuing as the direct pyramidal, or ventral cortico-spinal, tract, which finally crosses over in the spinal cord.

The **dorsal nuclei** include two new masses of gray matter, the **nucleus gracilis** and the **nucleus cuneatus** (Fig. 334), into which the long tracts of the dorsal columns of the cord (Goll and Burdach) are prolonged. The **gracile nucleus**, the first encountered in passing upwards, begins on a level

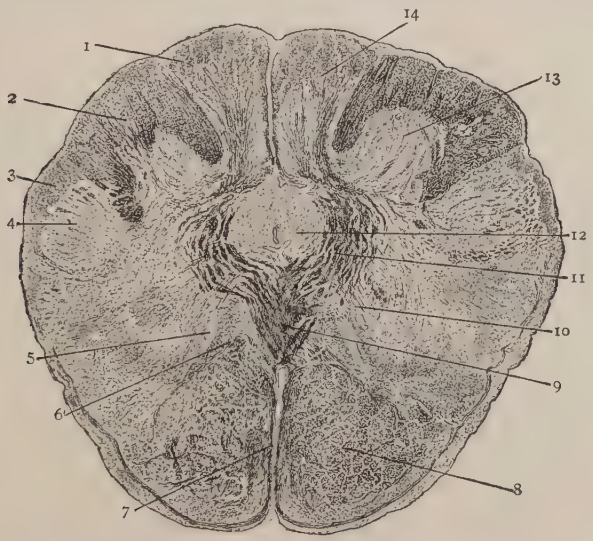


FIG. 334—Section across medulla a few millimeters above level A, Fig. 332, showing increased dorsal nuclei and substantia gelatinosa, sensory decussation and pyramidal tracts. 1, fasciculus gracilis; 2, fasciculus cuneatus; 3, spinal root of fifth nerve; 4, substantia gelatinosa; 5, accessory olivary nucleus; 6, fasciculus ventro-lateral ground-bundle; 7, superficial arcuate fibres; 8, pyramidal tracts; 9, sensory (fillet) decussation; 10, fibres of twelfth nerve; 11, deep arcuate fibres; 12, central gray matter, surrounding canal; 13, nucleus cuneatus; 14, nucleus gracilis. 5¼. (*Preparation by Professor Spiller.*)

with the pyramidal decussation and rapidly increases in bulk as the fibres of the fasciculus gracilis end around its cells. These neurones are multipolar and of varying size. Meanwhile the **cuneate nucleus** appears within the ventral part of the fasciculus cuneatus as an intrusive mass of gray matter, which soon becomes a prominent mottled area. This nucleus extends to a higher level than the nucleus gracilis.

Owing to the increased bulk of the fasciculi of the dorsal area occasioned by the appearance and expansion of the gracile and cuneate nuclei, the dorsal horns of the gray matter are displaced laterally and ventrally, so that they come to lie on a level with the central canal. Moreover, the dorsal cornua themselves, particularly the capping substantia gelatinosa, gain materially in bulk and now appear as two broad masses of gray matter (Fig. 334) that cause the dorso-lateral projections, the **tubercula Rolandi,**

seen on the surface. Beneath these elevations and closely overlying the areas of the substantia gelatinosa, a narrow lamina of longitudinally coursing nerve-fibres marks the position, one on each side, of the spinal or descending roots of the trigeminal nerves.

The chief purpose of the gracile and cuneate nuclei being the reception of the long afferent tracts continued from the cord and the distribution of impulses so received to the cerebellum and to the thalamus, new paths arise within these nuclei. About the level of the upper limit of the pyramidal decussation, axones of their neurones emerge from the gracile and cuneate nuclei as the **deep arcuate fibres,** sweep forwards and inwards in bold curves and cross the midline to the opposite side of the medulla. Most of them

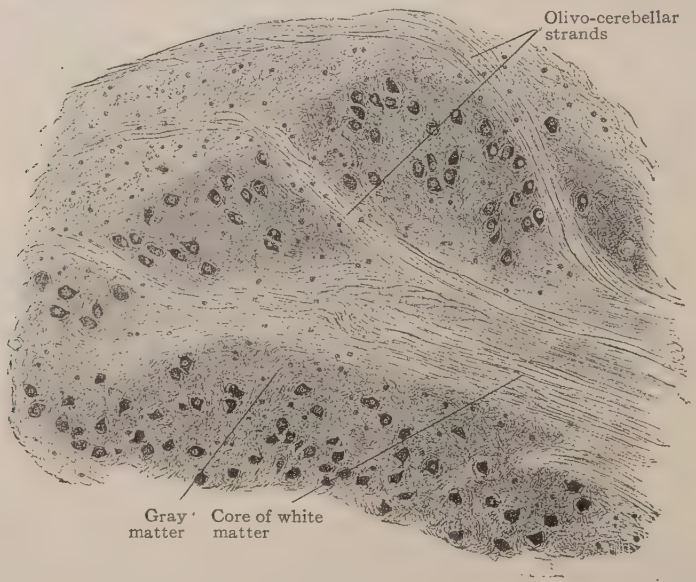


FIG. 335—Section of inferior olivary nucleus, showing plicated sheet of gray matter traversed by strands of nerve-fibres. × 100.

then turn sharply upwards and form the beginning of the important sensory pathway known as the **median fillet** (**lemniscus medialis**). The lowest fibres that cross in this manner constitute a fairly well defined strand, the **sensory decussation,** or **decussation of the fillet.** The crossing does not cease with this decussation, but, on the contrary, it is only the beginning of an extended series of afferent arcuate fibres that pass across the midline at various levels throughout the brain-stem. Since many longitudinal fibres are encountered by those sweeping from side to side, an interweaving of vertical and horizontal fibres takes place, which results in the characteristic **formatio reticularis** that constitutes a large area within the medulla (Fig. 336), as well as within the dorsal, or tegmental, portions of the pons and mid-brain.

The **olivary nuclei** include, in each half of the medulla, three masses of gray matter—the inferior olivary nucleus and the two accessory olivary

nuclei. The **inferior olivary nucleus** is a corrugated sac-like lamina of gray matter which underlies and causes the conspicuous oval elevation, the **oliva,** that occupies the upper half of the medulla at the outer side of the pyramid. In favorable cross-sections, the nucleus appears as a striking sinuous **C**-like figure (Fig. 336), the mouth of the sac (hilum) looking mesially. The greatest length of the nucleus is from 12–15 mm. and the transverse diameter about half as much. The plicated lamina of gray matter, from .2–.3 mm. thick, contains numerous, small, rounded neurones, from 18–26 μ in diameter, each provided with from three to five branched dendrites and an axone, embedded within a complex of axis-cylinders and neuroglia. The interior of the gray sac is filled with white matter, consisting of nerve-fibres, that

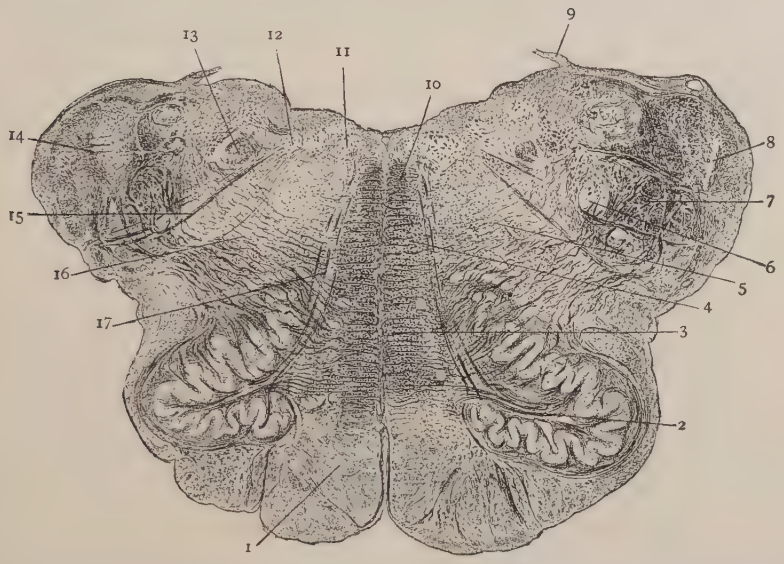


FIG. 336—Section across medulla at level B, Fig. 332; 1, pyramidal tracts; 2, inferior olivary nucleus; 3, median fillet in ventral area; 4, tecto-spinal tract; 5, formatio reticularis grisea; 6, 7, trigeminal nucleus and root; 8, restiform body; 9, torn ventricular roof; 10, median longitudinal bundle; 11, nucleus of XII and (12) of X nerve; 13, fasciculus solitarius; 14, dorsal area; 15, fibres of X nerve; 16, lateral area; 17, fibres of XII nerve. × 5. (*Preparation by Professor Spiller.*)

for the most part, stream through the hilum and constitute the **olivary peduncle.** The **accessory olivary nuclei** are two irregular plates of gray matter that lie median and dorsal to the chief olive. The **median nucleus,** 10–11 mm. long, is sagittally placed between the tract of the fillet and the root-fibres of the hypoglossal nerve. The **dorsal nucleus** is less extensive than the median and lies close to and behind the hilum of the inferior olive. In structure the accessory nuclei resemble the gray matter of the chief one.

The **central canal** and surrounding **gray matter** are gradually displaced dorsally within the closed lower half of the medulla in consequence of the increasing space required by the pyramids, the fillet-tract and the median longitudinal fasciculi—tracts that lie close to the median raphe and enlarge as they are followed upwards. Where the central canal opens out into the fourth ventricle, the surrounding gray matter is correspondingly

spread apart and becomes the lining of the ventricular floor (Fig. 336). Within this gray sheet and near the midline, on each side, lies the group of large, richly branched nerve-cells (40–70 μ) constituting the **hypoglossal nucleus,** from which arise the fibres of the twelfth cranial nerve. These strands take a direct ventro-lateral course through the medulla and emerge on the ventral surface in the groove between the pyramid and the olivary eminence. Slightly lateral, and to the outer side of the hypoglossal nucleus, another group of cells marks the position of the **dorsal vago-accessory nucleus.** These neurones are of small size (30–40 μ) and irregularly stellate or fusiform, and give origin to parasympathetic motor fibres of the tenth and bulbar portion of the eleventh cranial nerves. The root-fibres of the vagus traverse the medulla obliquely and meet the surface in the dorso-lateral groove marking the junction of the posterior and lateral divisions of the medulla.

In this way, the diverging fibres of the tenth and twelfth nerves sub-

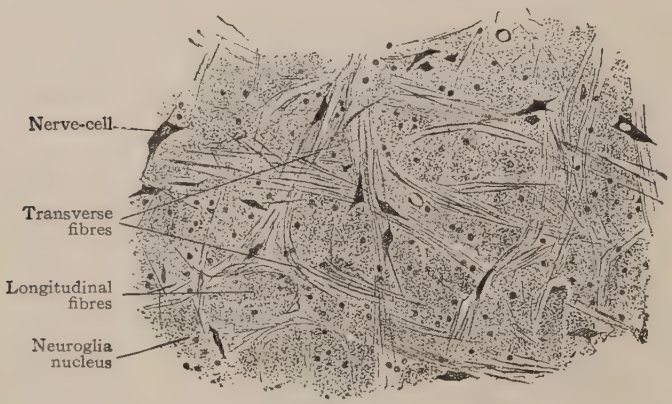


FIG. 337—Portion of formatio reticularis grisea of medulla. × 130.

divide each half of the medulla, as seen in transverse sections, into three triangular areas—the dorsal, the lateral, and the ventral.

The **dorsal area,** between the dorsal surface of the medulla and the vagus-fibres, contains a number of important fibre-tracts: (1) the **restiform body,** or inferior cerebellar peduncle, appears as a large tract of transversely cut fibres that occupies the greater part of the periphery. (2) The **descending root of the vestibular nerve** is seen as a field of loosely grouped bundles of cross-sectioned nerve-fibres to the inner side of the restiform body. (3) The **fasciculus solitarius** shows as a conspicuous transversely cut bundle that lies dorso-mesially to the vestibular root. (4) The **descending root of the trigeminal nerve** is readily identified as a superficial crescentic field enclosing on its mesial aspect the substantia gelatinosa.

The **lateral area,** between the diverging vagal and hypoglossal root-fibres, is occupied, in addition to (1) the **inferior olivary** and (2) the **dorsal accessory nucleus,** chiefly by the feltwork of fibres producing the formatio reticularis. In contrast to that within the ventral and mesial areas, the

reticulum of the lateral area contains considerable diffuse gray matter between its fibres and, hence, is known as (3) the **formatio reticularis grisea.** In this are irregularly distributed nerve-cells, for the most part large, and stellate or fusiform, as well as two more definite collections; one of these, (4) the **nucleus ambiguus,** consists of an inconspicuous group of large cells lying about the middle of the gray reticular substance; it is important as the ventral motor nucleus of the ninth and tenth nerves, giving origin to motor fibres supplying voluntary muscles. The other collection, (5) the **nucleus lateralis,** includes an uncertain aggregation of medium-sized cells situated near the periphery, ventral to the trigeminal root. A separate group of somewhat larger neurones, near the ventral border of the trigeminus, is the **nucleus lateralis dorsalis.**

The **ventral area,** between the midline and the hypoglossal root-fibres,

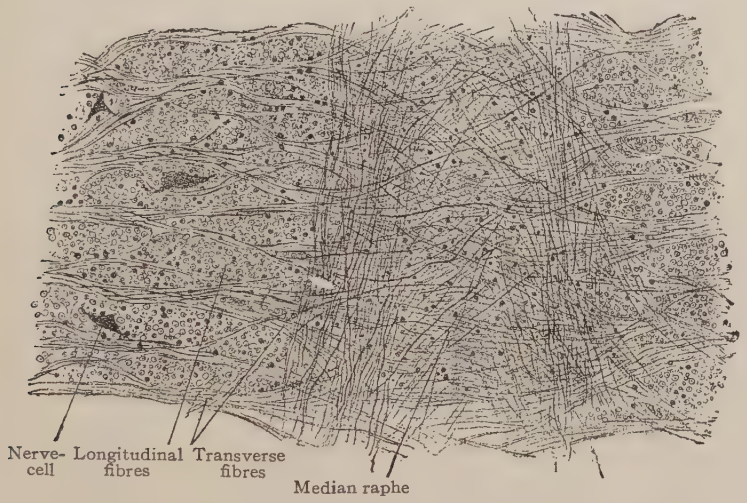


FIG. 338—Portion of formatio reticularis alba of medulla. × 130.

is occupied ventrally by (1) the **pyramidal tract,** which extends the entire width of the field. This zone is traversed by (2) the **ventral superficial arcuate fibres,** among which lies an irregular column of nerve-cells, (3) the **arcuate nucleus.** Dorsal to the pyramidal tract and next the midline, lies (4) the compact **tract of the median fillet,** composed of longitudinal strands that are the upward continuations of the deep arcuate fibres that at lower levels have bent brainwards, after crossing the midline. The fillet-tracts are also known here as the **interolivary stratum,** since they form a compact and compressed field between the inferior olivary nuclei. Between the fillet-tract and the hypoglossal fibres is (5) the **mesial accessory olivary nucleus.** (6) The **median longitudinal fasciculus** appears in cross-section as a compact strand, next the raphe and immediately beneath the gray matter of the floor of the fourth ventricle. The remaining space of the ventral field, between the pyramid and the ventricular gray matter, is occupied by (7) the **formatio reticularis alba,** so designated, in distinction to the formatio grisea,

on account of the preponderance of white matter and the small number of its nerve-cells, since with the exception of in the immediate vicinity of the midline where the **nucleus raphe** is found, these are almost wanting.

Although at higher levels additional and important masses of gray matter appear, especially those related to the auditory nerve, for the purpose of these pages, the foregoing general description of the medulla as seen in typical section, must suffice.

THE PONS VAROLII

Viewed from in front, the pons appears as a quadrilateral prominence, from 25–28 mm. long, interposed between the medulla below, the cerebral peduncles above, and the cerebellar hemispheres at the sides. Its lower

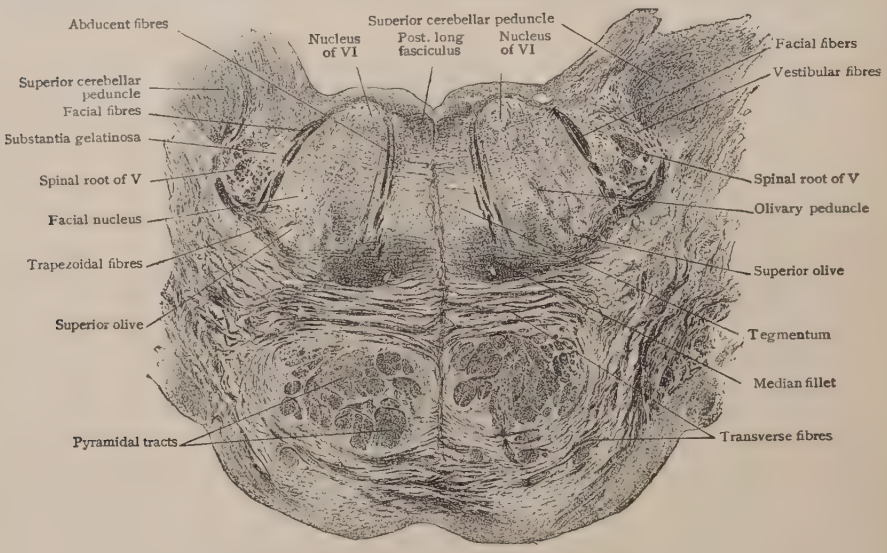


FIG. 339—Section across pons at level C, Fig. 332, showing subdivision into ventral and dorsal areas. × 3. (*Preparation by Professor Spiller.*)

and upper limits are well defined, but at the sides the narrowed mass of the pons is directly continued, downwards and backwards, into the cerebellum as **middle cerebellar peduncles.**

In transverse section (Fig. 339), the pons is seen to include two clearly defined areas, the ventral and the dorsal. The **ventral part,** or **pars basalis,** is largely occupied by the bulky pyramidal tracts, which are now excluded from the surface by a conspicuous layer of superficial transverse fibres, the **stratum superficiale pontis**. These transverse fibres, both superficial and deep, originate in cells of the pontile gray matter. For the most part, they cross the midline and continue laterally to form the middle cerebellar peduncles. They end within the cerebellar cortex. The pyramids, however, no longer appear as compact fields, as in the medulla, but are broken up into smaller bundles by the transverse strands of the **ponto-cerebellar fibres.**

At the upper border of the pons, the scattered pyramidal bundles become once more collected into two compact strands, which are continued into the cerebral peduncles. The dorsal limit of the ventral field is occupied by the **stratum profundum pontis,** a well marked layer of deep transverse fibres. A considerable amount of gray matter, collectively known as the **pontile nucleus,** is distributed within the interstices between the bundles of nerve-fibres. The numerous cells of this nucleus, generally small in size and stellate in form, are related to the ponto-cerebellar fibres of the same and

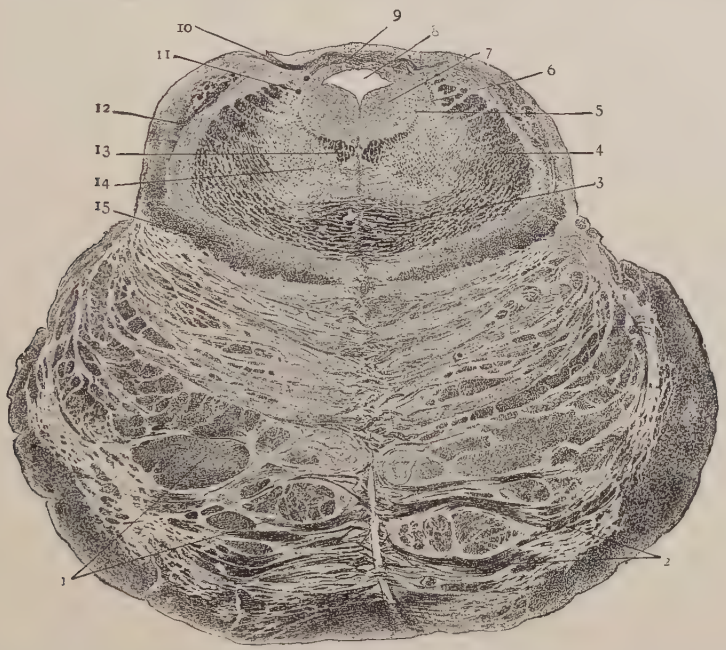


FIG. 340—Section across pons at level D, Fig. 332; 1, cortico-spinal and cortico-bulbar tracts; 2, transverse pontine fibres; 3, decussation and 4, arm of superior cerebellar peduncle; 5, nucleus and 6, mesencephalic root of V nerve; 7, gray matter surrounding 8, Sylvian aqueduct; 9, 10, 11, parts of IV nerve and its decussation; 12, lateral fillet; 13, median longitudinal fasciculus; 14, tegmental area; 15, mesial fillet. × 3. (*Preparation by Professor Spiller.*)

of the opposite side, many being stations of interruption in the cerebro-cerebellar paths.

The **dorsal,** or **tegmental, part** of the pons resembles in its general structure to a considerable extent the formatio reticularis grisea of the medulla, consisting for the most part of a reticulum of transverse and longitudinal fibres, interspersed with nerve-cells, on each side of the median raphe. The appearance of certain masses of gray matter and of nerve-fibres, together with changes in the position of the fillet, produces details that vary with the level of the section. When this passes just above the lower margin of the pons (Fig. 339), two diverging and obliquely cut strands of fibres mark the root-fibres of the sixth and seventh cranial nerves and divide the tegmental region, on each side, into three areas. The **middle area,** between the abducent fibres mesially and the facial ones laterally, contains three

important collections of nerve-cells. One of these, the **nucleus of the sixth nerve,** lies close to the floor of the ventricle and near the midline. The axones of these neurones, the root-fibres of the abducent (sixth) nerve, take a oblique ventral path and cut through not only the tegmental but also the ventral part of the pons to gain its lower border, along which they emerge. Another nucleus of the middle area, the **superier olivary nucleus,** lies laterally near the ventral limit of the tegmental area, partly lodged within an indentation on the dorsal aspect of the conspicuous tract of transverse fibres, the **corpus trapezoides.** This nucleus, often called the **superior olive** is an irregular spherical collection of neurones closely related with the tract of the **lateral fillet** and is thus part of the auditory pathways. A small collection of nerve-cells between the fibres of the trapezoidal tract constitutes the **nucleus trapezoides.** The **facial nucleus** is a broken mass of gray matter that includes several groups of large stellate motor neurones lying to the inner side of the emerging facial root-fibres.

The ventral part of the **inner area** and the adjoining portion of the middle one are occupied by the field of the **median fillet,** which, at the level under consideration, no longer lies with its long axis directed dorso-ventrally but approximately horizontal (Fig. 339). The tract now appears as a compressed and modified oval, with the thicker inner end close to the raphe and the tapering outer one near the superior olive. The **median longitudinal fasciculus** is seen as a compact strand, immediately beneath the gray matter of the ventricular floor and at the side of the raphe. Within the **outer area,** lateral to the facial fibres, appear the **substantia gelatinosa** and the associated **descending root of the trigeminal nerve.** Just dorsal to the latter, the **descending vestibular root** lies close to the inner side of the **restiform body.**

THE MID-BRAIN

The **mid-brain,** or **mesencephalon,** includes two main subdivisions: (1) the smaller dorsal part, the **quadrigeminal plate,** which roofs the Sylvian aqueduct and bears the corpora quadrigemina, and (2) the much larger ventral part made up by the the **cerebral peduncles,** or **crura cerebri.** The latter are further subdivided into two parts, a dorsal **tegmentum** and a ventral **basis pedunculi.** These are separated, in each lateral half of the peduncle, by the **substantia nigra,** a somewhat crescentic area of deeply-pigmented gray matter.

The **central gray matter** (**stratum griseum centrale**) encloses the Sylvian aqueduct and, along its ventral border, are the nuclei of the **oculomotor** and **trochlear nerves;** within its lateral parts lie the cells from which proceed the fibres of the mesencephalic roots of the trigeminal nerves.

The **substantia nigra** owes its color to the dark brown pigment within the cell-bodies. The **basis pedunculi,** the bold field that occupies the most ventral part of the peduncle (Fig. 342), consists chiefly of longitudinal fibre-tracts, which are passing from the cerebral cortex, by way of the internal capsule, to lower levels in the brain-stem and the spinal cord. The longitudinal fibres are separated into bundles by the invasion of numerous strands from the fibre-complex known as the **stratum intermedium,** which lies along the

ventral border of the substantia nigra. The **fibres of the basis** include three general sets: (1) the **cortico-pontile fibres,** passing from the cells of the cerebral cortex to the cells of the pontile nucleus as links in the cortico-cerebellar paths; (2) the **cortico-bulbar fibres,** passing as axones from the motor neurones of the cerebral cortex to the nuclei of motor fibres originating within the pons and medulla; (3) the **cortico-spinal fibres,** passing as axones from the cerebral motor neurones, through the ventral tracts of the brain-stem into the pyramidal tracts of the spinal cord, to end around the radicular cells.

The **tegmentum** of the mid-brain includes, as seen in transverse sec-

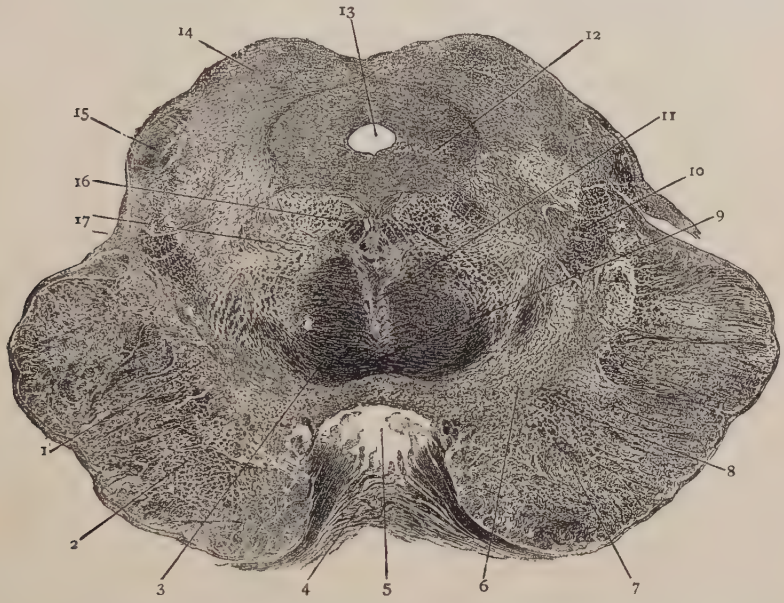


FIG. 341—Section across brain-stem (mid-brain) at level E, Fig. 332. 1, substantia nigra, separating basis pedunculi from tegmentum; 2, basis pedunculi; 3, superior cerebellar peduncle and (9) its decussation; 4, uppermost fibres of pons; 5, interpeduncular space; 6, substantia nigra; 7, motor tracts in basis; 8, stratum intermedium; 10, mesial fillet; 11, fountain decussation of tecto-spinal tract; 12, central gray substance; 13, Sylvian aqueduct; 14, inferior colliculus of corpora quadrigemina; 15, inferior quad. brachium; 16, median longitudinal fasciculus; 17, tegmental field. × 3. (*Preparation by Professor Spiller.*)

tions (Fig. 341), the area bounded by the corpora quadrigemina dorsally and the crescents of the substantia nigra ventrally. In the vicinity of the central gray matter, the tegmentum consists chiefly of a **reticular foundation** resembling the formatio reticularis seen at lower levels. In other parts of the tegmentum are the prominent fibre-tracts belonging to the **mesial** and **lateral fillets** and the **superior cerebellar peduncles** and the large rounded masses of gray matter, the **red nuclei** (nucleus ruber).

The **nucleus ruber,** or **nucleus tegmenti,** (Fig. 342) is of ovoid form and reddish tint when fresh, and consists of a complex of gray matter and nerve-fibres. The latter preponderate below, where the red nucleus receives the fibres of the superior cerebellar peduncle, but are much less numerous above, since many fibres come to an end around the rubral neurones.

These elements are very variable in size (20–60 μ) and shape, but are mostly irregularly triangular or stellate. The red nuclei not only constitute important stations in the path connecting the cerebellum with the spinal cord (**cerebello-rubro-spinal fibres**), but also contribute links in the chain uniting the **corpus striatum** with the cord (**striato-rubro-spinal fibres**). While some of the constituents of the superior cerebellar peduncle pass around the red nucleus and continue as the **cerebello-thalamic fibres** uninterruptedly to the

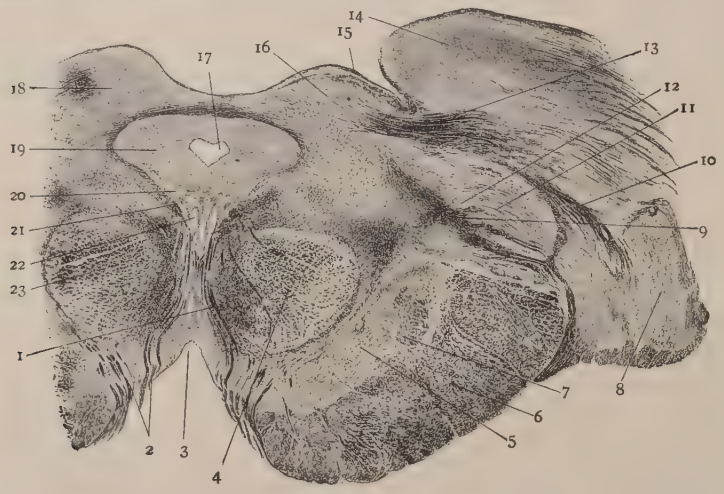


FIG. 342—Section across brain-stem (mid-brain) at level F, Fig. 332. 1, 2, root-fibres of oculomotor nerve; 3, interpeduncular space; 4, red nucleus; 5, substantia nigra; 6, crusta of cerebral peduncle; 7, stratum intermedium; 8, lateral geniculate body; 9, fillet fibres; 10, superior quad. brachium; 11, median geniculate body and (12) its nucleus; 13, optic fibres; 14, pulvinar of optic thalamus; 15, stratum zonale of (16) superior colliculus; 17, Sylvian aqueduct; 18, sup. colliculus; 19, central gray substance; 20, 22, nucleus of oculomotor nerve; 21, median longitudinal fasciculus; 23, red nucleus. × 2¾. (*Preparation by Professor Spiller.*)

optic thalamus, the majority of the fibres of the peduncle end around the neurones of the nucleus, from which then proceed axones as the **rubro-thalamic fibres.** It is important to remember that, in a general way, the ventral part of the brain-stem transmits the great efferent, or motor, paths, while within the dorsal, or tegmental, part ascend the chief afferent, or sensory, tracts. The median longitudinal fasciculus serves as an association-path linking together the nuclei of the cranial nerves, and connecting them with the vestibular system, through axones from Deiter's nucleus.

THE CEREBELLUM

The cerebellum occupies the posterior fossa of the skull and lies behind the pons and medulla and the fourth ventricle (Fig. 331). It consists of a median lobe, the **vermis,** and of two **lateral hemispheres.** The latter attain a very large size in man. By means of its three peduncles—inferior, middle, and superior—the cerebellum is connected with the medulla, the pons, and the mid-brain, respectively. Its surface is divided by the deeper fissures into **lobules,** each of which is subdivided by shallower clefts into narrow tracts,

the **folia,** from 2–4 mm. wide, that, within a given lobule, in a general way parallel one another.

The free surface of the cerebellum is everywhere covered by a continuous sheet of **cortical gray matter** which follows and encloses the subdivisions of the **medullary layer.** The latter, as exposed in sagittal sections, appears as a compact central mass of white matter, from which stout stems radiate into the various lobules. From these primary stems, secondary branches penetrate the subdivisions of the lobules, and from the sides of these, in turn, smaller tracts of white matter, the tertiary branches, enter the individual folia. Over these ramifications of the white core, the cortical gray matter stretches as a fairly uniform layer that closely follows the complexity of the folia and fissures. The resulting arborization and the contrast between

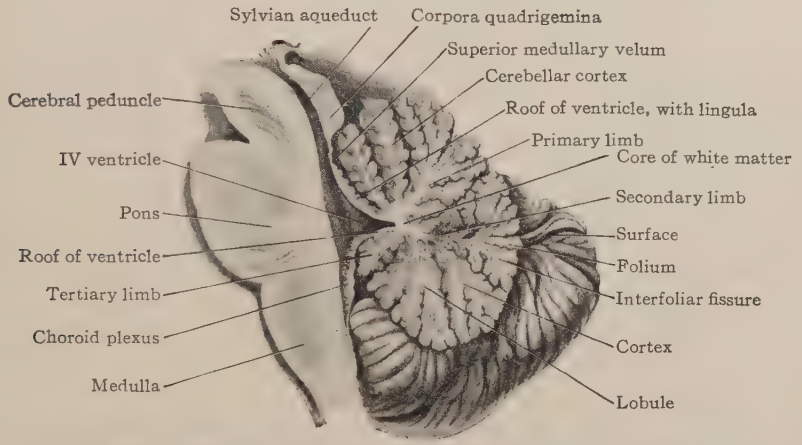


FIG. 343—Mesial sagittal section of brain-stem and cerebellum, showing fourth ventricle and relations of the central white matter and its limbs to the continuous sheet of gray cortex.

the white and gray matter, best seen in sections passing at right angles to the folia, produce a picture known as the **arbor vitæ cerebelli.**

The Cerebellar Cortex.—The cortical gray matter (Fig. 344) includes two very evident strata–the outer and lighter **molecular layer** and the inner and darker **granule layer.**

The **molecular layer** is of uniform thickness, about .4 mm., and contains three varieties of nerve-cells: the Purkinje cells, the basket-cells, and the small cortical cells. The **Purkinje cells,** the most distinctive elements of the cerebellum, occupy the deepest part of the molecular layer, where they are disposed in a single row along the junction of the outer and inner layers. The cells are more numerous and are closely placed upon the summit of the folia than along the fissures, in which latter situation they are often less typical. They possess a large flask-shaped body, about 60 μ in diameter, from the pointed and outwardly directed end of which usually a single robust **dendrite** arises. This chief dendrite, relatively thick and very short, divides into two branches, which at first diverge and run more or less horizontally and then turn sharply outwards to assume a course vertical to the

surface and to undergo repeated subdivision. The arrangement of the larger dendrites is very striking and recalls the branching of the antlers of a deer. The smaller processes arise at varying and often acute angles, the completed branching resulting, as seen in silver preparations (Fig. 345), in an arborization of astonishing richness and extent, that may reach almost to the outer boundary of the molecular layer. The branching of the dendrites of each cell is in one plane only; the branching is not like that of a tree standing in the open field, but is like a vine growing on a wall. This plane is in the direction across the folia. It follows that only in sections transverse to the folia do these arborizations show their full extent. In sections parallel

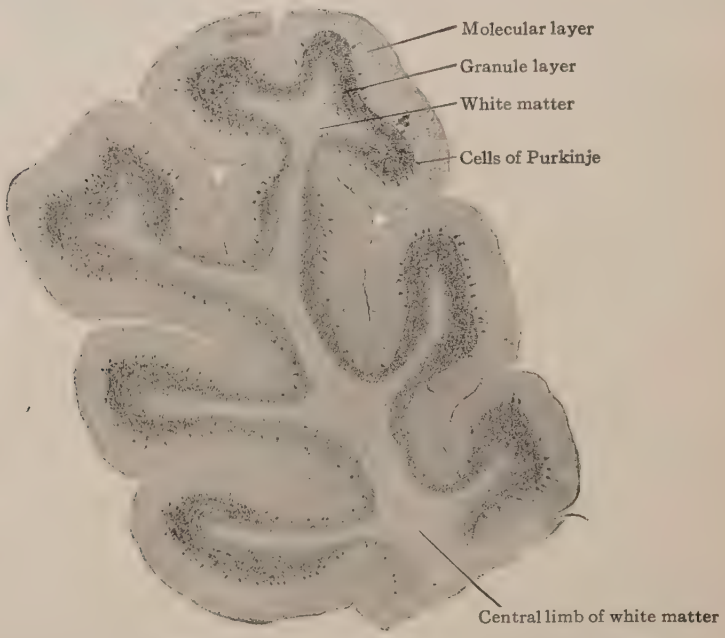


FIG. 344—Section across cerebellar folium, showing relations of cortex to underlying white matter. × 10.

to the length of the folia, the arborization appears very narrow, as shown in the accompanying diagram (Fig. 346). The **axone** of the Purkinje cell arises from the rounded basal, or deeper, end of the body and at once enters the subjacent granule layer, which it traverses to gain the white medullary substance of the folium. It then continues to one of the internal nuclei of the cerebellum (**e.g.** nucleus dentatus). The axones of the Purkinje cells constitute the pathway for practically all impulses leaving the cerebellar cortex. During their early course the axones give off a few recurrent collaterals that return to end in little terminal enlargements upon adjacent Purkinje cell-bodies.

The **basket-cells** lie chiefly within the deeper half of the molecular layer. They possess an irregular stellate body (10–20 μ), from which several dendrites radiate. Their chief feature is the axone, which extends

across the folium above the Purkinje cell-bodies. During this course, the axone gives off from three to six collaterals that descend to the cells of Purkinje, whose bodies they surround and enclose with a basket-like arborization, the terminal ramification of the main process itself ending in like manner. By this arrangement each basket-cell is brought into close relation with several of the Purkinje cells, an association probably of consequence in spreading out impulses and in insuring coördination.

The **small cortical,** or **superficial, stellate cells** are smaller than the basket-cells, and are scattered in the outer part of the molecular layer. Both axone and dendrites are short and branching.

The **granule layer,** of a rust-brown tint when fresh and deeply colored in stained preparations, is thickest on the summit of the folia and thinnest opposite the bottom of the fissures. It is more sharply demarcated from the overlying molecular layer than from the subjacent white matter. The granule layer contains two varieties of nerve-cells—the granule cells and the large stellate cells.

FIG. 345—Purkinje cell from human cerebellar cortex; silver preparation; *a*, axone. × 180.

The **granule cells** are very small (7–10 μ) and numerous and so closely packed that they confer a distinct density on the stratum, of which they are the chief components. They are provided with from three to six short radiating dendrites that end in peculiar claw-like arborizations (Fig. 346) in relation with other granule cells. Their axones directed towards the surface, enter the molecular layer, within which they undergo **T**-division at various levels, corresponding to the depth at which the cells lie. The two resulting branches run horizontally and lengthwise in the folium, that is, parallel to the surface and at right angles to the plane of greatest expansion of the Purkinje dendrites, through whose arborizations they find their way and with which they probably come into close relation. The axones apparently end free and without arborizations.

The **large stellate cells** (**large association cell, Golgi type II**) are present in varying number, but are never many. They lie close to the outer limit of the granule layer and possess a cell-body of irregular form, 30–40 μ in diameter, from which usually several richly branched dendrites pass in different directions, but largely into the molecular layer. The axone is most

distinctive since very soon after leaving the cell-body it splits up into an arborization of unusual extent and complexity, which, however, is confined to the granule layer. These cells, therefore, belong to type II. Since their processes are brought into intimate relation with a number of other neurones these elements are association cells. Additional nervous elements within the granule layer, few in number and fusiform in outline, are described as the **solitary cells,** concerning which little is known. All of the cells described above, except the Purkinje cells are **association cells** of the cortex.

The **cortical nerve-fibres** include three chief varieties. (1) The **axones of Purkinje cells** contribute an inconsiderable portion of the fibres passing between the cerebellar cortex and medullary substance. They end, for the

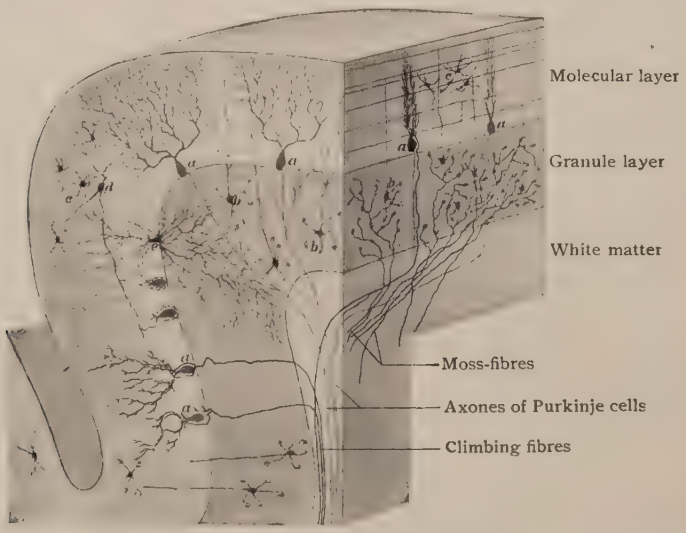


FIG. 346—Diagrammatic reconstruction of part of folium, illustrating relations of nerve-cells and fibres of cerebellar cortex; transverse (left) and longitudinal (right) cut surfaces of folium are shown; *a*, Purkinje cells; *b*, granule cells; *c*, small cortical cells; *d*, basket-cells; *e*, large association cell of type II.

most part, in the dentate nucleus within the white core near the root of the superior cerebellar peduncles, some in the smaller internal nuclei, and some perhaps, in relation with the cells of the vestibular and inferior olivary nuclei. (2) The so-called **moss fibres,** which ascend from the medullary into the granule layer, within the latter repeatedly branch and bear moss-like tufts that end in large part in irregular small masses of stainable substance, known as the **eosin-bodies,** that lie between the granule cells (Fig 347). According to Cajal, these bodies are formed by the intricate interlacement of the terminal ramifications of the afferent axones, of the dendrites of the granule cells and also of the axones of the Golgi cells. In view of their convoluted complexity they have been called the **glomeruli** of the cerebellum. Other filaments of the moss-fibres are continued into the molecular layer, bending horizontally and repeatedly branching. (3) The **climbing-fibres** ascend through the granule to the molecular layer, where their tendril-like ramifications entwine and cling to the principal dendrites of the Purkinje cells.

Additional fibres within the granule layer are, evidently the axones of the granule cells and the collaterals of the cells of Purkinje, whilst a large proportion of the fibres within the molecular layer are the ramifications of the axones of the granule, the basket and the smaller cortical cells.

The **moss-fibres** and **climbing fibres** are the terminals of fibres which convey impulses into the cerebellar cortex. Their cells of origin are situated in widely distant regions of the spinal cord and brain-stem. Thus from the spinal cord come spino-cerebellar tracts; from the inferior olivary nuclei come olivo-cerebellar fibres; from the pons come ponto-cerebellar fibres; and from the vestibular nuclei come vestibulo-cerebellar fibres. These and others are parts of pathways conveying proprioceptive impulses, which have the ultimate origin in tendons, muscles, joints, and the vestibular apparatus (semicircular canals, etc.).

The **neuroglia** forms a supporting framework of considerable density within both the cortex and the medulla. In preparations colored with nuclear stains, the neuroglia cells are conspicuous within the granule layer, to whose numerous small nuclei they materially contribute. A number of relatively large neuroglia cells lie within the outer part of the granule layer, near the Purkinje cells; in addition to short and irregular centrally directed processes, these elements give off brush-like groups of fibres which penetrate the molecular layer, seldom branching, as far as the surface of the folium, where they end in minute triangular expansions. By the apposition of the latter a delicate subpial condensation, a sort of limiting membrane, is produced. The radial disposition of the neuroglia fibres, as well as of the Purkinje dendrites, climbing fibres and larger blood-vessels, confer upon the molecular layer a vertical striation. Other neuroglia cells, stellate with spider-like radiating fibres, occupy all levels of the molecular layer; similar cells, with more extended processes, occur between the nerve-fibres of the medullary substance.

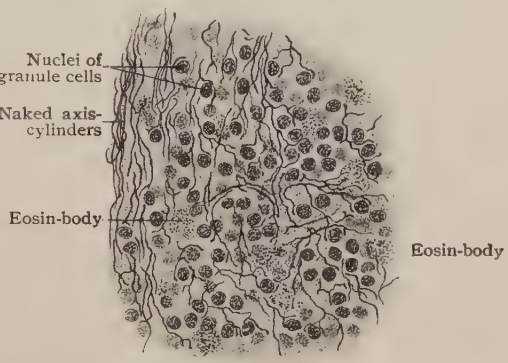


FIG. 347—Portion of granule layer of young cerebellum, showing eosin-bodies and nerve-fibres. × 220.

The Internal Nuclei.—There are four paired masses of gray matter, the internal nuclei—one of considerable size and the others small—embedded within the central white matter of the cerebellum.

The **nucleus dentatus,** or **corpus dentatum,** the largest and most important of the internal nuclei (Fig. 348), consists of a plicated sac of gray matter, enclosing nerve-fibres, and resembles in many respects the inferior olivary nucleus. It lies within the anterior part of the median half of the hemisphere and measures from 15–20 mm. in its longest dimension.

Of the other paired internal collections of gray matter—the nucleus

fastigii, the nucleus emboliformis, and the nucleus globosus—the **nucleus fastigii,** or the **roof-nucleus,** is the best defined. It is an egg-shaped mass, about 10 mm. long, and lies within the core of the vermis close to the mid-line and to its fellow of the opposite side.

The **nucleus emboliformis** and the **nucleus globosus** are irregular masses of gray matter lying between the dentate and roof-nuclei, with which they are respectively united, as well as with each other.

In **structure** the internal nuclei differ markedly from the cerebellar cortex, since in the main they are composed of irregularly disposed nerve-cells of one kind, interspersed with nerve-fibres. The **dentate nucleus** contains cells (20–30 μ), angular or stellate in outline and pigmented. Their

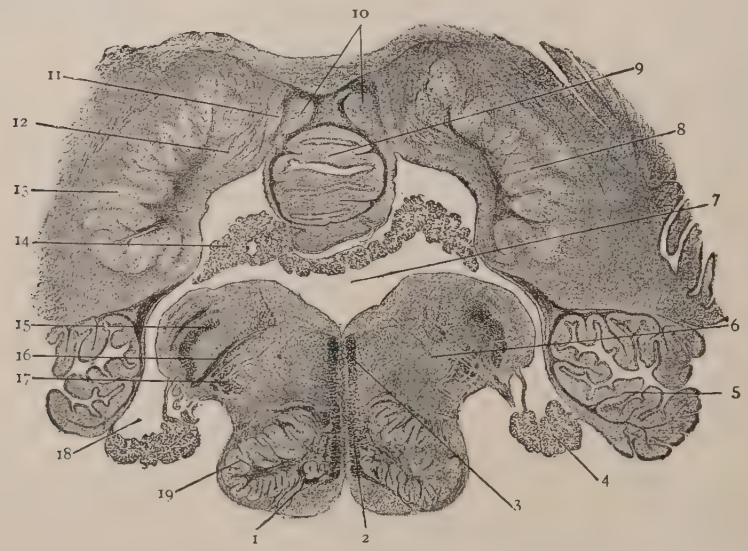


Fig. 348—Transverse section through fourth ventricle and surrounding parts of brain-stem and of cerebellum and its internal nuclei: 1, pyramidal tracts; 2, mesial fillet; 3, median longitudinal fasciculus; 4, choroid plexus; 5, cerebellar folia; 6, medulla; 7, fourth ventricle; 8, nucleus dentatus; 9, inferior vermis; 10, nucleus fastigii or roof-nucleus; 11, nucleus globosus; 12, nucleus emboliformis; 13, nucleus dentatus; 14, choroid plexus; 15, inferior cerebellar peduncle; 16, fibres of vagus nerve; 17, spinal root of fifth nerve; 18, lateral recess of IV ventricle; 19, inferior olivary nucleus. × 3½. (*Preparation by Professor Spiller.*)

processes are usually so disposed that the axones pass into the medullary substance enclosed by the plicated lamina and the dendrites into the surrounding white matter of the hemisphere. Numerous fibres enter the dentate body from without, many being the axones of Purkinje cells. Since the nuclei emboliformis and globosus are only incompletely separated parts of the dentate nucleus, their structure corresponds closely with that of the chief mass. The **roof-nuclei** on the contrary, possess cells of much larger size (40–80 μ), more rounded form, and greater uniformity in tint, although they are distinctly pigmented. Numerous strands of nerve-fibres subdivide the nucleus into secondary areas, while some large, transversely coursing bundles establish a decussation with the roof-nucleus of the opposite side. The

dentate and roof-nuclei are important stations, since from their cells arise the fibres composing the greater part of the superior cerebellar peduncles.

The **course** of **nervous impulses through the cerebellar cortex** may follow several paths. The most direct would be through climbing fibres to Purkinje cells, and out again by axones of Purkinje cells to one of the internal cerebellar nuclei. Another, less direct, circuit would be through moss fibres, granule cells, **T**-shaped axones of granule cells to dendrites of Purkinje cells, thence through Purkinje cell-bodies and axones to one of the internal nuclei. The cells within the latter contribute the axones which make up the superior cerebellar peduncles, carrying on the impulses to the red nuclei of the mid-brain, to the thalamus, and to the medulla.

THE CEREBRUM

The cerebrum—the "great brain" as distinguished from the cerebellum—comprises in a general way, the large hemispheres and the parts surrounding the third ventricle. These correspond to the **telencephalon** and **diencephalon** of the fetal brain. The much-folded surfaces of the cerebral hemispheres are invested with a continuous sheet of gray matter, the **cerebral cortex.** The cortical sheet varies in thickness not only in the same area, being thicker over the summit than along the sides of the convolutions or

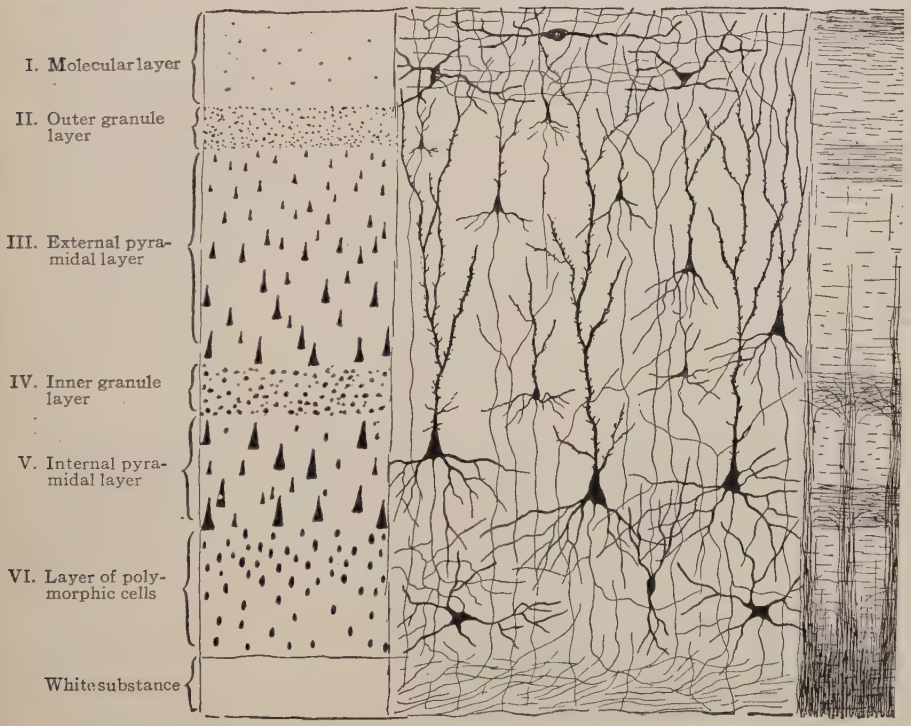


FIG. 349—Schematic representation of the structure of the cerebral cortex. (*Villiger.*)

at the bottom of the fissures, but in different regions. Its average thickness is about 3 mm., but where it borders the upper end of the Rolandic fissure, this increases to almost 5 mm., whilst over the occipital poles the thickness of the cortex is reduced to about 2 mm. The entire superficial extent of the cortex has been estimated to be about 2000 sq. cm., of which scarcely one-third is exposed surface, the remainder being sunken. According to Donaldson, the cortex contributes about one half of the weight of the brain.

FIG. 350—Section of cerebral cortex. ×90.

The essential histological elements of the cerebral cortex are the nerve-cells and the nerve-fibres. No single method of preparation suffices to display satisfactorily both groups of structural elements, for when stains are employed which best bring out the cells, the fibres are inadequately shown; and, conversely, when methods adapted for the demonstration of the fibres are followed the cells are but imperfectly displayed. It is advantageous, therefore, to study the histological details of the brain by more than a single method, combining the results obtained by the use of cellular stains with those yielded by procedures exhibiting the fibres. Among the latter, the well-known method of Weigert, or its modifications, has been of great service in extending our knowledge concerning the various fibre-tracts. The methods of silver impregnation introduced by Golgi and extended by Ramón y Cajal, although not producing true staining but only incrustations of the cell and its processes, have greatly advanced our knowledge concerning the form of the cell-bodies and the number and extent of the processes of the neurones.

While varying as to details in different regions, the cerebral cortex presents a general plan of structure which may be considered: (**a**) in relation to the nerve-cells and (**b**) in relation to the nerve-fibres.

The Nerve-Cells of the Cortex.—When sections cut perpendicular to the surface of the convolution are stained with basic stains (Fig. 350) or prepared after silver impregnation (Fig. 351), the cerebral cortex exhibits usually six principal layers, which, from without inwards, are: (1) the stratum zonale, (2) the outer granule layer, composed principally of many granule-like cells, (3) the external pyramidal layer, mostly of medium-sized pyramidal cells, (4) the inner granule layer, a very narrow band, characterized by small stellate cells, (5) the internal pyramidal layer of many medium-sized and large cells, among which, especially in the precentral motor area, are scattered very large pyramidal cells, and (6) the layer of polymorphic cells. Although each presents characteristics which are distinctive, with the exception of the junction between the first and second layers where the change is well defined, no sharp demarcation separates the strata, each passing insensibly into the adjoining layer. Neither are the modifications which distinguish the cortex of certain regions abruptly assumed, one type of cortical structure being gradually replaced by another without sudden transition.

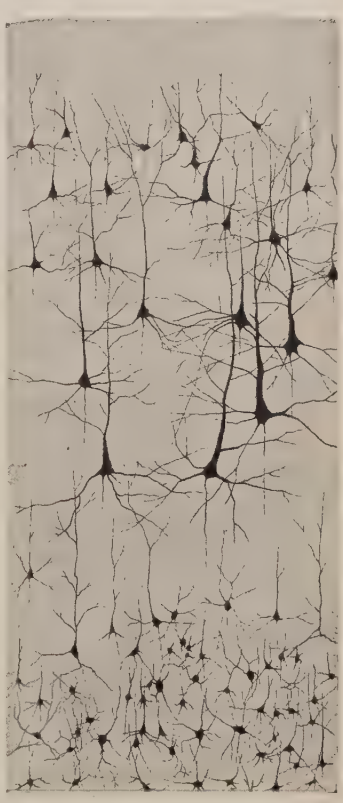


FIG. 351—Nerve-cells of cerebral cortex, after silver impregnation. × 70. (*Preparation by Prof. T. G. Lee.*)

The **stratum zonale (molecular layer),** underlies the pia and measures about .25 mm. in thickness. The layer contains few nerve-cells and appears subdivided into (**a**) a narrow peripheral zone, from 10–30 μ in width, composed of a subpial condensation of neuroglia and (**b**) a deeper zone characterized by many myelinated fibres which course parallel to the surface, and a meagre number of nerve-cells whose most distinctive representatives are small fusiform elements, (**Cajal's cells**) provided with long tangentially directed processes. With the latter intermingle the numberless terminal processes of the pyramidal and other cells lying at deeper levels and fibres which continue from the white core of the gyrus into the outermost layer of the cortex.

The **outer granule layer** is marked off from the stratum zonale with some distinctness since, in contrast to the last-mentioned zone, it contains very many cells. These are of small size (7–10 μ) and in the superficial part

are rounded or irregularly triangular, but they assume the distinctive pyramidal outline as they approach the subjacent layer, whose elements they resemble in possessing apical and lateral processes.

The **external pyramidal layer** contains larger cells than the preceding. They are of typical pyramidal shape, and are mostly of medium size with some large ones intermingled in the deeper part. The latter are especially evident in the temporal region.

The **inner granule layer** is a narrow zone of small stellate cells interposed between the external and internal pyramidal layer. It is lacking in the precentral region. Its small multipolar cells have short axones and belong to Golgi's type II. In this stratum is the outer stripe of Baillarger.

The **internal pyramidal layer** (*ganglionic layer* or *layer of large pyramidal cells*), contains the most distinctive neurones of the cerebral cortex. The cells increase in size, but diminish in numbers as they are traced inwards, the largest (20–40 μ in width) and most characteristic lying in the deepest part of the stratum. In the motor (precentral) convolution, the largest elements are called the cells of Betz, the axones of which form the cortico-bulbar and cortico-spinal tracts, which extend to the brain-stem and spinal cord. The typical pyramidal cell possesses a conical body, triangular in section, the apex of which is continued into a long tapering dendrite, the **apical process,** which extends towards the periphery. Upon gaining the stratum zonale the process breaks up into a number of end-branches that run parallel with the surface and contribute to the fibre-complex of the outer layer. During its course to the surface, the apical dendrite gives off a number of branches that extend horizontally and, with the collaterals and similarly directed processes from other cells, take part in producing the feltwork giving rise to a thin light band, known as the **outer stripe of Baillarger.** From the deeper or basal surface of the cell arises the delicate centrally-directed **axone,** which acquires a myelin sheath and enters the white matter. The axone gives off one or more **collaterals** which establish relations with other and often remote cells. In addition to the two chief processes, the peripherally directed apical dendrite and the centrally coursing axones, a variable number—from four to twelve—of secondary **lateral dendrites** spring from the basal angles of the cell. These processes usually divide dichotomously, each succeeding pair of branches in turn splitting into twigs, until the dendrite is resolved into an end-brush of fibrillæ which aid in producing an intricate feltwork of finest threads. Each pyramidal cell contains a conspicuous spherical or ellipsoidal nucleus, within which a distinct nucleolus is usually distinguishable. The cytoplasm exhibits a striation and, in addition to the masses of tigroid substance, the Nissl bodies, a mass of brownish pigment granules. The larger pyramidal cells are surrounded by an evident pericellular space.

The **layer of polymorphic cells** includes many small nerve-cells, from 8–10 μ in diameter, whose forms vary greatly, irregular, spherical, triangular, stellate, and fusiform elements being present. Small pyramidal cells are also often seen within this layer. The radial disposition of the groups of fibres within the deepest stratum of the cortical substance limits the polymorphic

cells chiefly to the interfascicular areas within which the cells consequently appear arranged in a somewhat columnar order.

Within the deeper layers of the cortex among the pyramidal and the polymorphic cells are the cells of Martinotti and the cells of Golgi's type II. The latter which are most abundant in the inner granule layer are also found scattered singly. Although both dendrites and axones undergo elaborate arborization, they are confined to a limited territory in the vicinity of the cell-body, and the axones, therefore, do not reach the stratum zonale.

The **cells of Martinotti** are of small size and triangular or spindle-form in outline and particularly distinguished by the unusual direction of their axones. These processes pass towards the surface, and within the stratum zonale divide into branches which are continued horizontally in the feltwork of tangential fibres.

Neuroglia cells are present in all parts of the cerebral cortex and, while in a general way they send fibrils in all directions between the nervous elements, which they then support, the arrangement of the fibrillæ is fairly definite in certain strata. Thus within the subpial condensation of the neuroglia the glia cells send most of their processes as inwardly directed brushes. The cells within the deeper part of the cortex give off their processes in two chief groups, one extending towards the periphery and the other towards the white core.

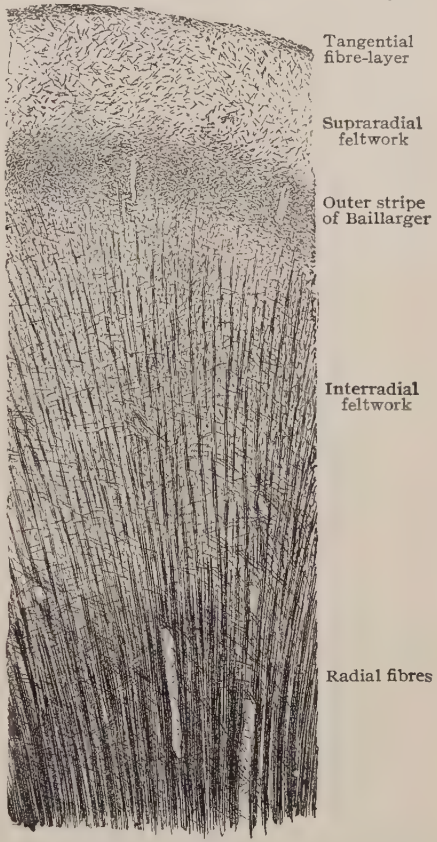


FIG. 352—Section of cerebral cortex stained to show nerve fibres; the cells are not seen but lie between the strands of fibres. × 21.

The Nerve-Fibres of the Cortex.—When viewed in suitably stained sections cut parallel with their general course, the cortical nerve-fibres do not appear as a uniform layer, but as radially disposed bundles which gradually become less distinct as they traverse the cortex and finally disappear at about the level of the outer border of the layer of large pyramidal cells. The **radial fibres** are partly afferent and partly efferent. The **corticofugal components,** which predominate are largely the centrally directed axones of the pyramidal and the polymorphic cells which are continued as the fibres composing the subcortical white matter. The peripherally coursing axones of the cells of Martinotti also contribute to the production of the fibre-radii. The **corticopetal constituents** of these tracts include the nerve

fibres which are derived from cells situated more or less remote. Such, for example, are the thalamo-cortical and the tegmento-cortical fibres, as well as the many commissural fibres that arise in the opposite hemisphere and cross by way of the corpus callosum. Although for the most part the corticopetal fibres end at various levels in arborizations around the pyramidal cells, some are continued into the stratum zonale where they assist in producing the tangential zone.

The spaces between these radial bundles are occupied by a delicate interlacement, the **interradial feltwork,** which is composed in large part of the lateral and collateral processes of the cells. Within the fourth layer, the horizontally coursing collaterals and processes of the subjacent large pyramidal cells form a complex of unusual intricacy, which condensation gives rise to the outer stripe of Baillarger. Beyond the outer ends of the radial fibre-bundles, the intercellular ground-work is occupied by a second delicate interlacement of processes and collaterals, the **supraradial feltwork;** while immediately beneath the narrow subpial neuroglia zone innumerable delicate terminal fibrillæ course horizontally and parallel with the surface and constitute the **tangential fibre-layer.** The components of this layer are the terminal branches of the dendrites of the pyramidal and polymorphic cells and the axones of the cells of Martinotti as well as the main and secondary processes of the fusiform elements of the stratum zonale.

Local Variations in the Cerebral Cortex.—While in the main certain features are common to the cortex wherever well developed, more or less evident variations occur in different localities. Such variations depend upon the size and number of the nerve-cells and the richness and direction of the nerve-fibres—changes which produce alterations in the relative proportions of the strata. The width of the stratum zonale is almost constant and subject to little modification, being usually well defined from the outer granule layer. The internal pyramidal layer, on the contrary, exhibits considerable variation, either in increased thickness, as in the precentral gyrus, or in diminished breadth, as in the occipital lobe. The layer of polymorphic cells is fairly uniform, but within the precentral convolutions is reduced almost to disappearance, although the pyramidal cells of the superimposed layer are here of unusual size. Such variations in the histological features of the cortex are probably correlated with differences in the function of its various regions, although the exact relations between such differences are in many cases still obscure. Disregarding the cortical regions which are profoundly modified by their rudimentary character, such as the olfactory lobe, apart from minor variations in details, the cortex of the greater part of the frontal, parietal, occipital, temporal, and limbic lobes, and of the insula closely corresponds in its structure. That of the motor (Rolandic) region, of the calcarine (visual) area of the occipital lobe, and of the hippocampus, dentate gyrus, and adjacent part of the hippocampal gyrus, however, presents very evident modification.

The **Rolandic cortex** of the precentral gyrus—the great cortical motor area of the hemisphere—is distinguished by the unusual size of some of the large pyramidal cells and the feeble development of the layer of polymorphic cells. The pyramidal cells,

collectively tend to larger size as the upper end of the precentral convolution is approached and, in addition, cells of extraordinary dimensions appear. These elements, the **giant pyramidal,** or **Betz's, cells,** reach their maximum size within the paracentral lobule, where some attain a breadth of 65 μ, or almost double that of the pyramidal elements in other regions. The giant cells are further distinguished by their robust and rounded form, their distribution in small groups of from three to five in the deeper layers of the cortex, and the exceptional thickness of their axones.

The Internal Nuclei.—Embedded within the white matter of the cerebrum, for the most part completely separated from the cortex, lie certain paired masses of gray matter collectively known as the **basal ganglia.** These include: the two parts of the corpus striatum, the **caudate** and **lenticular nuclei,** the **claustrum,** the **amygdaloid nucleus,** and the **thalamus.** Of these, two, the corpus striatum and the thalamus, will be briefly described.

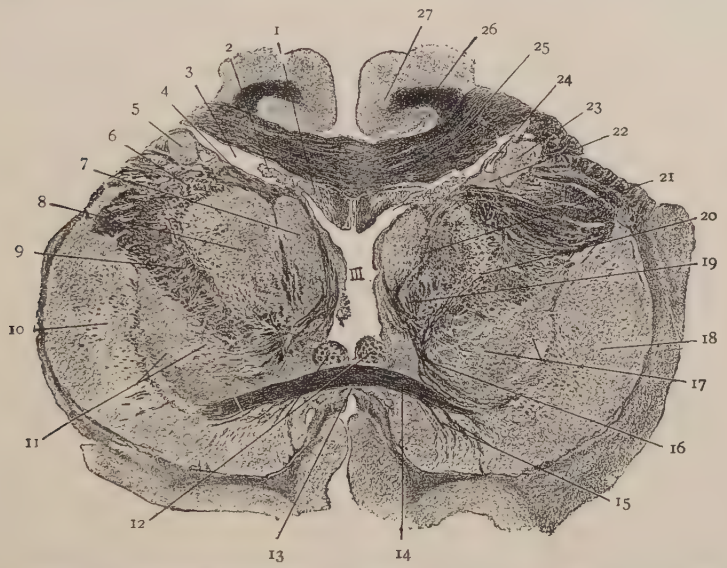


FIG. 353—Portion of oblique frontal section of cerebrum, showing the ventricles, the basal ganglia (caudate and lenticular nuclei and optic thalami) and the internal capsule. 1, fornix, below corpus callosum (25); 2, choroid plexus; 3, lateral ventricle; 4, stratum zonale; 5, caudate nucleus; 6, internal capsule, knee; 7, mesial and (8) lateral nucleus of thalamus; 9, internal capsule; 10, putamen and (11) globus pallidus of lenticular nucleus; 12, anterior pillars of fornix; 13, lamina terminalis; 14, anterior commissure; 15, olfactory fibres; 16, thalamo-tegmental tract; 17, globus pallidus; 18; putamen; 19, mammillo-thalamic tract; 20, external and (21) internal medullary lamina; 22, stria terminalis, 23, caudate nucleus; 24; striate vein; 25, corpus callosum; 26, cingulum; 27, gyrus callosus. × ½. (*Preparation by Professor Spiller.*)

The Corpus Striatum.—This large mass of gray matter, which extends from the outer wall of the lateral ventricle to almost the cortex, consists of two parts, the **caudate nucleus,** or inner division, and the **lenticular nucleus,** or outer division. Although continuous in front and below, the two parts are separated almost completely by the intervening important tract of white matter, the **internal capsule,** which is the great pathway for nerve-fibres between the cerebral cortex and the lower portions of the central nervous system. The caudate nucleus is an elongated comet-shaped mass of gray matter, well seen from the lateral ventricle. The lenticular

nucleus lies to the outer side of the internal capsule and is subdivided by two narrow tracts of white matter, the **medullary laminæ,** into three segments. Of these the outer one, the **putamen,** is the darkest and closely corresponds in structure with the nucleus caudatus. The middle and inner zones together constitute the **globus pallidus** and are lighter in tint, owing to the excessive number of pervading bundles of nerve-fibres. Morphologically and developmentally the nucleus caudatus and putamen are similar and represent the newer part of the corpus striatum, or **neostriatum,** while the globus pallidus is the **palæostriatum** corresponding to the corpus striatum found in lower vertebrates.

The **cells** of the neostriatum are of both small and large varieties. The small cells are mostly of Golgi's type II, with short axones. The large cells

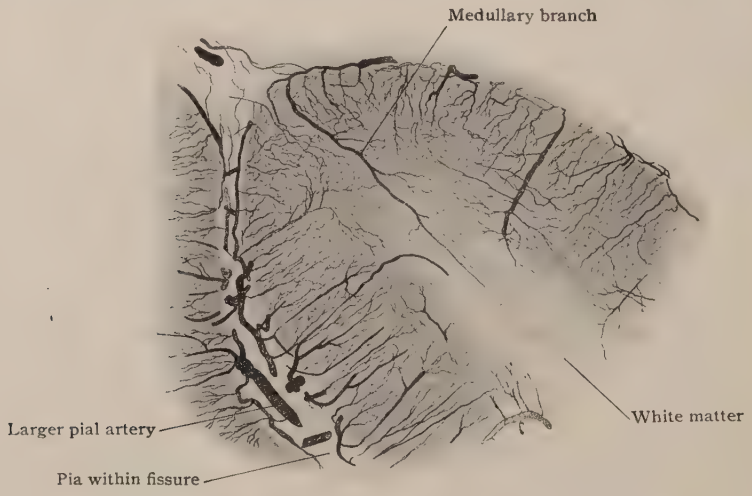


FIG. 354—Injected cerebral cortex, showing capillary supply of gray and white substance. × 18.

contribute **internuncial fibres,** which connect the several regions of the striatum. The characteristic cells of the palæostriatum are large cells (35–70 μ) of a motor type. They have long axones which form the efferent fibre-system, **ansa lenticularis,** running to the substantia nigra, subthalamic nucleus, and red nucleus, as well as to the thalamus. The functions of the corpus striatum are connected with the tonus of muscles, especially with the control of automatic associated movements. Lesions of the striatum are found in cases of paralysis agitans and in chorea. The neostriatum is mostly inhibitory and coördinating in function, while the palæostriatum is motor efferent, forming part of the extrapyramidal motor system.

The Thalamus.—This large ovoid ganglionic mass lies between the third ventricle mesially of which cavity it constitutes the lateral wall, and the internal capsule laterally. Its free dorsal surface, and to a less degree the mesial as well, is covered with a thin layer of nerve-fibres, the **stratum zonale,** while ventro-laterally the thalamus is separated from the internal

capsule by a denser layer of fibres, the **external medullary lamina.** The gray matter is subdivided into three general parts, the **lateral,** the **mesial,** and the **anterior nucleus,** by a vertical sheet of white matter, the **internal medullary lamina,** which splits anteriorly into two sheets to include the anterior nucleus. Of these three, the lateral nucleus is the largest and includes the **pulvinar** of the thalamus. The **neothalamus** comprises the large lateral nucleus with pulvinar, together with the geniculate bodies. The **palæothalamus** includes the mesial and anterior nuclei, and in addition, the subthalamic nucleus of Luys. The latter is largely connected with the extrapyramidal system. The thalamus not only constitutes a great relay station for somatic afferent impulses, but also is a sensory centre for the **affective** qualities of sensation, **i. e.,** whether painful or agreeable. The nerve-cells of the thalamic nuclei include three chief varieties: (1) the **stellate cells** (35–50 μ), distinguished by their richly branched dendrites

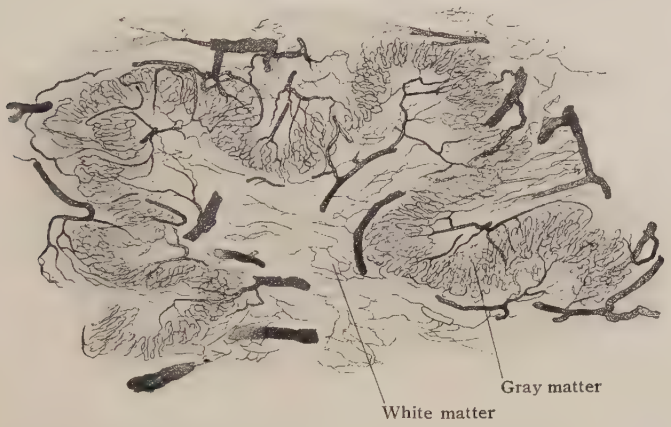


FIG. 355—Injected dentate nucleus of cerebellum, showing rich capillary supply of plicated gray matter. × 20

that radiate in all directions; (2) the **brush-cells,** so called on account of the brush-like expansions of their dendrites, spindle or triangular and from 20–40 μ in diameter; and (3) the **polygonal cells,** few but large (50–60 μ), with a number of long slender tortuous dendrites. The thalamic cells are by no means uniformly distributed, but, on the contrary, are aggregated into larger and smaller groups, the **subsidiary nuclei;** of these nine are distinguished by Malone, by whom they are described according to the types of cells and their grouping. Of these the **ventro-lateral nucleus** is of especial importance, since it receives the afferent fibres of the great sensory pathways, the medial fillet and spino-thalamic tracts. In a general way, the neurones of the thalamus may be regarded as receptors of a large part of the afferent impulses carried to the cerebrum from the cerebellum, brain-stem, and spinal cord, such impulses being distributed by the **thalamo-cortical fibres,** the axones of the thalamic cells, to the cerebral cortex.

Blood-Vessels of the Brain.—The **arteries** supplying the brain are derived from the internal carotid and vertebral stems. Their immediate

distribution to the cerebral and cerebellar cortex is everywhere through the agency of the pia mater, within which the larger trunks, after frequent anastomoses, give off the abundant small **end-arteries** that penetrate the subjacent nervous substance. On entering the gray matter, these **cortical branches,** whose general course is parallel to one another and at right angles to the surface, break up into rich networks of capillaries. The vascular supply of the gray matter is more generous than that of the white substance, which latter receives, however, in addition to continuations from the cortical capillary network, a number of **medullary branches.** These contribute few twigs to the gray substance, but traverse the latter and have their chief distribution as long-meshed capillary networks within the white matter. The arteries are accompanied by connective tissue envelopes, prolonged from the pia mater, which enclose ensheathing **perivascular spaces.**

The **cortical veins** begin in the white matter and pass through the gray sheet to reach the pia mater, within whose external part they ramify, the arteries usually lying deeper. The larger emergent stems, however, do not follow the main branches of the cerebral arteries, but converge towards the lines of the principal adjacent dural sinuses into which they open. The cerebral veins are among those possessing little or no muscular tissue and no valves.

True **lymphatics** are found neither within the brain nor spinal cord. Extensions of the subarachnoid spaces are represented by the **perivascular spaces** surrounding the blood-vessels within the nervous substance; and the **pericellular spaces** enclosing the large nerve-cells.

THE MENINGES

The entire cerebro-spinal axis is surrounded by three membranes, or meninges. These are: (1) an external dense fibrous membrane, the **dura mater,** which is closely attached directly to the inner surface of the skull and in the vertebral canal forms an independent loose sheath for the spinal cord; (2) an internal connective tissue tunic, the **pia mater,** which contains the blood-vessels supplying the nervous tissue and, therefore, is adherent to every part of the free surface of the brain and spinal cord; and (3) an intermediate delicate non-vascular membrane, the **arachnoid,** which usually lies close to the dura and varies in its relation to the pia mater.

Between the dura and the arachnoid lies a narrow, for the most part capillary cleft, the **subdural space,** which contains a small quantity of clear straw-colored fluid, of the nature of lymph. The arachnoid and the pia mater are separated by a much larger cavity, the **subarachnoid space,** which in certain places, especially on the basal surface of the brain, reaches extensive dimensions. It contains the **cerebro-spinal fluid,** that is usually limpid or slightly yellowish and may show a very few lymphocytes (estimated normally as five cells per cubic millimeter of fluid). The cerebro-spinal fluid is produced within the brain-ventricles, from the tufts of blood-vessels of the several choroid plexuses and, after filling the ventricular spaces and the central canal of the cord, escapes through the thin roof of the fourth ventricle into the subarachnoid spaces.

The Dura Mater.—Within the skull, the membrane (**dura mater encephali**), consists of an **outer** and an **inner layer.** The former replaces the periosteum and is intimately attached to the bones to which it carries nutritive blood-vessels (branches of the meningeal arteries). The inner layer forms the incomplete fibrous partitions, as the falx and tentorium, which separate and support the several subdivisions of the brain. Along the attachments of these partitions, the inner layer splits to form the walls of the large venous spaces, the **dural sinuses,** which are lined with endothelium and constitute the channels into which the blood returned by the veins from the nervous tissue is poured.

Within the vertebral canal, the dura (**dura mater spinalis**), forms a loose sac for the cord which corresponds to a prolongation of the inner cranial layer. It loses its intimate relation to the bones at the foramen magnum and lies with the vertebral canal often separated from the periosteum by considerable tracts of areolar tissue.

In **structure,** the dura consists of closely placed bundles of unusually rigid fibrous tissue, intermingled with elastic fibres. Although the latter exist in considerable numbers, especially in the inner layer of the brain-dura, they are so overshadowed by the preponderance of the fibrous tissue that the membrane as a whole is relatively inelastic. Within the outer layer in the skull, the fibres pursue a general antero-lateral to postero-medial direction while those of the inner layer follow an opposite, antero-medial to postero-lateral course. Within the spinal sac, their disposition is chiefly longitudinal. The connective tissue cells are represented by flattened plate-like elements between the fibrous bundles and some plasma cells in the vicinity of the blood-vessels. The inner surface of the dura, the outer wall of the subdural space, is covered by a continuous layer of endothelial cells. The existence of isolated patches of endothelium on the outer surface of the membrane within the skull, is regarded as evidence of the existence of limited **epidural spaces.**

The **blood-vessels** of the brain-dura, not taking into account the large venous sinuses, are all branches from the various meningeal arteries. In addition to supplying the dural tissue, their purpose is to provide nourishment to the bones of the cranium, which, therefore, are the objective distribution for the larger part of the terminal vessels. The outer layer, being virtually the periosteum, contains many more vessels than the inner, the larger trunks showing as elevated ridges on the cranial surface. Meningeal veins are also present, but, in many cases, do not accompany the arteries and pursue an independent course. The spinal dura contains comparatively few blood-vessels.

The **nerves** within the dura are numerous and include two sets—those destined for the walls of the blood-vessels, more plentiful, and sympathetic in character, and those, the less numerous nervi proprii, containing sensory fibres derived from the cranial and spinal nerves. They end in free filaments or in bulbous expansions.

The Pia Mater.—This membrane, the vascular tunic, lies in contact with all parts of the cerebro-spinal axis, and, since it contains the blood-vessels supplying the nervous substance, accurately follows all the irregu-

larities of the surface of the brain, with its many convolutions and fissures, and of the spinal cord. Additionally, in certain places where the wall of the brain-tube is always very thin, the pia pushes before it the attenuated brain-layer and seemingly gains entrance into the ventricles. Examples of such invagination are afforded in the relations of the velum interpositum and the choroid plexuses to the lateral and third ventricles and of the similar plexuses in the roof of the fourth ventricle. The pia mater further contributes a sheath to each nerve, or its larger component bundles, as the nerve leaves the brain or spinal cord, which sheath surrounds the nerve as it crosses the subarachnoid space and for a variable distance beyond its emergence from the dural sac.

The **spinal pia** consists of two layers, of which the dense outer is composed of interlacing stout bundles of fibrous tissue mixed with elastic fibres and covered externally by endothelium, and the looser inner one of less closely packed fibro-elastic strands. These layers are separated here and there by tissue-clefts and enclose between them the blood-vessels. The latter subdivide within the pia into numerous small arteries which, although the larger trunks frequently anastomose, enter the subjacent nervous substance as "end-arteries," each providing the entire available blood-supply for a definite territory.

FIG. 356—Small portion of injected choroid plexus of lateral ventricle; surface view. × 25.

The **brain-pia** consists of only a single layer which corresponds to the inner one of the spinal membrane both in structure and relations. The larger vessels lie in or on its outer part and in certain places where they are of large diameter, as at the base of the brain, project within the subarachnoid space, although covered by a thin envelope of pial tissue. As the vessels penetrate the nervous tissue, they carry with them a sheath of pia mater, at first loosely but later closely applied. These constitute the **perivascular sheaths** that follow the arteries to their smallest ramifications, but are finally lost. Since the arteries entering the nervous tissue, especially the cerebral and cerebellar cortex, are very abundant, collectively a considerable amount of connective tissue is carried with the vessels into gray matter, the larger vascular septa containing fibro-elastic tissue as well as neuroglia. The ultimate distribution of the arteries entering the spinal cord, and the brain is described in connection with those organs. In certain locations, particularly the base of the brain and over the cervical and lumbar enlargements of the cord, the pia sometimes, especially in aged subjects, contains deeply pigmented branched connective tissue cells.

The **choroid plexuses** of the ventricles comprise two morphologically distinct parts—the vascular pial tissue and the thin covering of brain-wall. The vascular fringes consist of numerous capillary convolutions, the **choroidal glomeruli,** from 1–2 mm. in diameter, embedded in the pial connective tissue stroma and covered with a single layer of cuboid ependymal cells. The latter contain fat and pigment particles and during fetal life bear cilia.

The numerous **nerves** within the pia mater are chiefly sympathetic fibres destined for the walls of the blood-vessels. Within the skull they are derived chiefly from the plexuses surrounding the internal carotid and vertebral arteries; within the spinal pia they are contributed, usually, from the gray sympathetic rami. Additional nerve-fibres, probably sensory in function, occur in small numbers. Their mode of termination is uncertain, although free and bulbous endings have been described.

The Arachnoid.—The intermediate membrane is, for the most part, a thin connective tissue envelope that intervenes between the dura and the pia and, notwithstanding its delicacy, completely separates the subdural from the subarachnoid space. It contains neither blood-vessels, lymphatics, nor nerves and consists of an interlacement of flattened bundles of fine fibrous tissue interspersed with elastic fibres and plate-like cells. In addition to the main sheet, the partition, both sides of which are covered with endothelium, numerous trabeculæ extend across the subarachnoid space and in places are so plentiful as to convert the cleft into a sponge-like structure. In contrast to the pia mater, which closely follows the surface of the brain and cord, the arachnoid is separated from the cerebro-spinal axis and its immediate covering by a more or less extensive space. Over the convexities of the convolutions, however, the arachnoid and the pia are fused into a single membrane; elsewhere the subarachnoid space, filled with cerebro-spinal fluid, is considerable and on the basal surface of the brain very extensive and represented by the **cisternæ.**

The cerebro-spinal fluid escapes into the dural sinuses not only by lymph-paths along the nerve-trunks and larger veins, but also by filtration through local tuft-like accumulations of arachnoid tissue, situated particularly along the superior longitudinal sinus. These tufts known as the **Pacchionian bodies,** consist of spongy masses of arachnoid tissue, covered externally with endothelium, which push before them the greatly attenuated dura and, overlaid by the latter and the endothelial lining of the blood-space, project into the sinus or its lateral diverticula. By this arrangement the cerebro-spinal fluid that occupies the interstices of the arachnoid tissue filters through the interposed structures and finds its way into the venous current within the dural sinuses.

THE ORGANS OF THE SENSES

The cells directly receiving the stimuli producing the sensory impressions of touch, smell, taste, sight, and hearing are all derivations of the ectoderm—the great primary sensory layer from which the essential parts of the organs of special sense are differentiations. The olfactory cells—nervous elements that correspond to ganglion-cells—retain their primary relation, since they remain embedded within the invaginated peripheral epithelium lining the nasal fossæ, sending their dendrites towards the free surface and their axones into the brain. Usually, however, the nerve-cells connected with the special sense-organs abandon their superficial position and lie at some distance from the periphery, receiving the stimuli not directly, but from the epithelial receptors by way of their dendrites. In the case of the most highly specialized sense-organs, the eye and the ear, the percipient cells lie enclosed within capsules of mesodermic origin, the stimuli reaching them by way of an elaborate path of conduction.

THE SKIN

Since the extensive integumentary sheet that clothes the exterior of the entire body not only serves as a protective investment, an efficient regulator of body temperature, and an important excretory structure, but also contains the special end-organs and the peripheral terminations of the sensory nerves that receive and convey the stimuli producing tactile, temperature, and pain impressions, the skin may be appropriately considered along with the other sense-organs. On the other hand, the correspondence of its structure with that of the mucous membranes, with which it is directly continuous at the orifices on the exterior of the body, emphasizes the close relation of the skin to the alimentary and other mucous tracts.

This general investment, the **tegmentum commune,** includes the **skin proper** with the specialized tactile corpuscles, and its **appendages**—the **hairs,** the **nails,** and the **cutaneous glands.** Its average superficial area is approximately one and a half square meters.

The **skin** (**cutis**), using the term in a more restricted sense as applied to the covering proper without its appendages, everywhere consists of two distinct portions, a superficial **epithelial** and a deeper **connective tissue stratum,** which are derivatives of the ectoderm and the mesoderm, respectively. The former, the **epidermis,** is devoid of blood-vessels, the capillary loops never reaching farther than the subjacent **corium,** as the outermost layer of the connective tissue stratum is called. The **thickness** of the skin, from .5–4 mm., varies greatly in different parts of the body, being least on the eyelids, penis, and nymphæ, and greatest on the palms of the hands and soles of the feet and on the shoulders and back of the neck. Of the entire thickness, the proportion contributed by the epidermis is, in most localities, about .1 mm.

The Connective Tissue Stratum.—The connective tissue stratum, usually much the thicker portion of the skin, includes two layers, the **corium** and the **tela subcutanea,** which, however, are so blended with each other as to be without sharp demarcation.

The **corium,** or **derma,** the more superficial and compact of the connective tissue layers, lies immediately beneath the epidermis from which it is always well defined. With the exception of within a few localities, as over the forehead and the external ear, the outer surface of the corium is not even but is beset with elevations, ridges, or papillæ, which produce corresponding modelling of the opposed under surface of the overlying epidermis. The best developed papillæ are on the flexor surfaces of the hands and feet, where

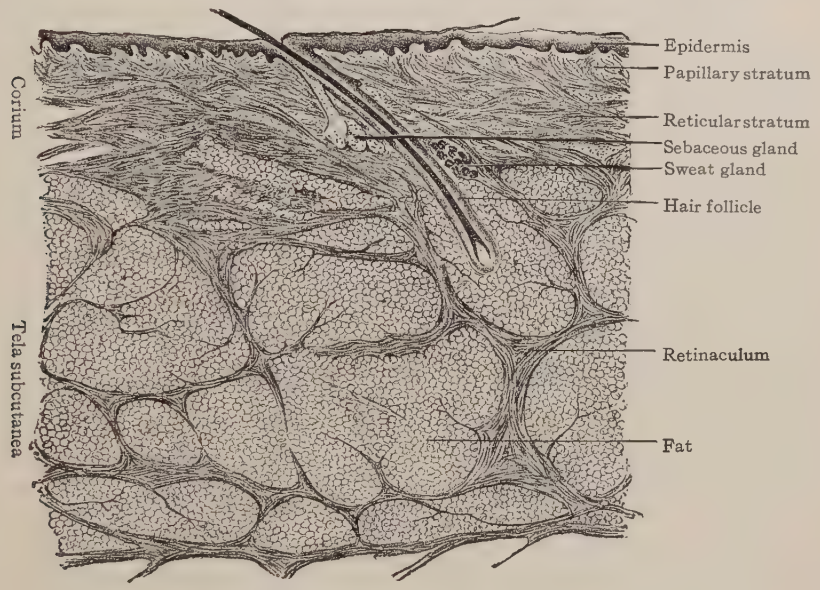


FIG. 357—Section of skin, showing its chief layers—epidermis, corium and tela subcutanea. × 17.

they attain a height of .2 mm. or more and are disposed in the closely set double rows that underlie the **cutaneous ridges** on the palms and soles. The patterns formed by the cutaneous ridges remain throughout life unchanged and, as seen in imprints of the fingers, are so distinctive for each individual that they afford a reliable and practical means of identification. The markings of the two hands are symmetrical and sometimes identical. The papillæ afford favorable positions for the lodgement of the terminal capillary loops and the special organs of touch; they are accordingly grouped as **vascular** and **tactile.**

The corium is subdivided into an outer **papillary stratum** containing the papillæ, and a deeper **reticular stratum** composed of the closely interlacing bundles of fibrous and elastic tissue that are continued into the more robust and loosely arranged trabeculæ of the tela subcutanea. The strata of

the corium, however, are so blended that they pass insensibly and without definite boundary into each other. Although composed of the same histological factors—bundles of fibrous tissue, elastic fibres, and connective tissue cells—their disposition is much more compact in the dense reticular stratum than in the papillary layer. While the general course of the fibrous bundles within the corium is parallel or oblique to the surface, some strands, continued upwards from the underlying subcutaneous sheet, are vertical and traverse the stratum reticulare either to bend over and join the horizontal bundles, or to break up and disappear within the papillary stratum. The elastic tissue, which constitutes a considerable part of the corium, occurs as fibres and networks. Within the reticular stratum these form robust tracts corresponding with the general arrangement of the fibrous bundles. Towards the surface of the corium, the elastic fibres become finer and more branched and beneath the epidermis anastomose to form the delicate but close **subepithelial elastic network.**

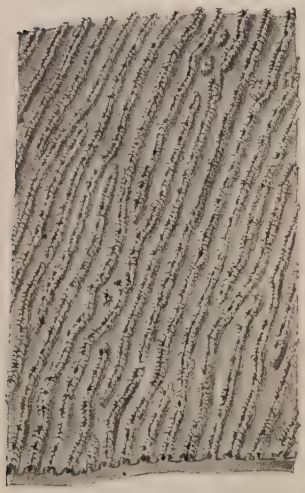


Fig. 358—Portion of corium from palmar surface of hand after removal of epidermis; each range includes a double row of papillæ, which underlie the surface ridges and the openings of the sweat-glands; the latter appear as dark points along the ranges of papillæ. × 5.

The **tela subcutanea,** the deeper layer of the connective tissue portion of the skin, varies in its thickness and in the density and arrangement of its component bundles of fibro-elastic tissue, with the amount of fat and the number of hair-follicles and glands lodged within its meshes. The latter are irregularly round and enclosed by tracts of fibrous tissue, some of which known as the **retinacula cutis** are prolonged from the corium to the deepest parts of the subcutaneous stratum. Here they often blend into a thin but definite sheet, the **fascia subcutanea,** which forms the innermost boundary of the skin and is connected with the subjacent structures by strands of areolar tissue. Where such loose connection is wanting, as on the scalp, face, palms, and soles, the skin is intimately bound to the underlying muscles, or fasciæ, and lacks the independent mobility that it elsewhere enjoys. The integument covering the eyelids and penis is peculiar in retaining to a conspicuous degree its mobility although devoid of fat. Where the latter is present in large quantity the term **panniculus adiposus** is often applied to the tela subcutanea.

In places in which the skin glides over unyielding structures, the interfascicular tissue-spaces of the tela subcutanea may undergo enlargement and fusion, resulting in the production of the subcutaneous **mucous bursæ.**

In addition to the strands of **involuntary muscle** associated with the hair as the arrectores pilorum, unstriped muscular tissue is incorporated with the skin in the mammary areolæ and over the scrotum, and penis (tunica dartos). The facial muscles having largely cutaneous insertions, the skin covering the

face is invaded by tracts of striated muscular tissue that penetrate as far as the corium.

The Epidermis.—The epidermis, or **cuticle,** the outer portion of the skin, consists entirely of epithelium and, being partly horny, affords protection to the underlying corium with its vessels and nerves. The thickness of this layer varies in different parts of the body. Commonly from .08—.10 mm., it is greatest on the flexor surfaces of the hands and feet, where it

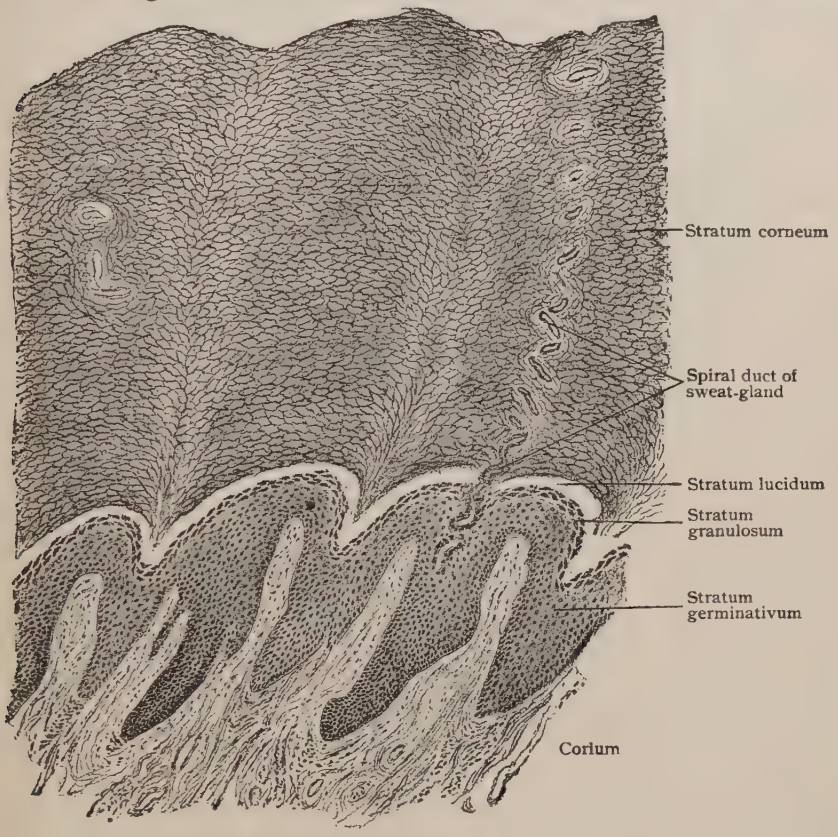


Fig. 359—Section of skin from sole of foot, showing layers of epidermis. × 70.

reaches from .5–.9 mm. and from 1.1–1.3 mm. respectively. Where exposed to unusual pressure, as on the palms of laborers or on habitually unshod soles, the epidermis may attain a thickness of 4 mm.

The cuticle consists of two chief layers, the deeper **stratum germinativum,** containing the more active elements, and the **stratum corneum,** the cells of which undergo cornification. Between these layers lies a third, the **stratum intermedium,** that is ordinarily represented by only a single row of cells to which the name **stratum granulosum** is usually applied. This layer marks the level at which the conversion of the epithelial elements into horny plates begins and also that at which the separation effected by blistering

usually occurs. On the palms and soles, where the epidermis attains not only great thickness but also higher differentiation, an additional layer, the **stratum lucidum,** making four in all, may be recognized. The first two represent the portion of the epidermis endowed with the greatest vitality and powers of repair and the last two the horny and harder part.

The **stratum germinativum,** or **stratum Malpighi,** rests upon the outer surface of the corium, by the papillæ of which it is impressed and, hence, when viewed from beneath after being separated, commonly presents a more or less evident network of ridges and enclosed pits, the elevations corresponding to the interpapillary furrows and the depressions to the papillæ. In recognition of this reticulation the name, **rete Malpighi,** is

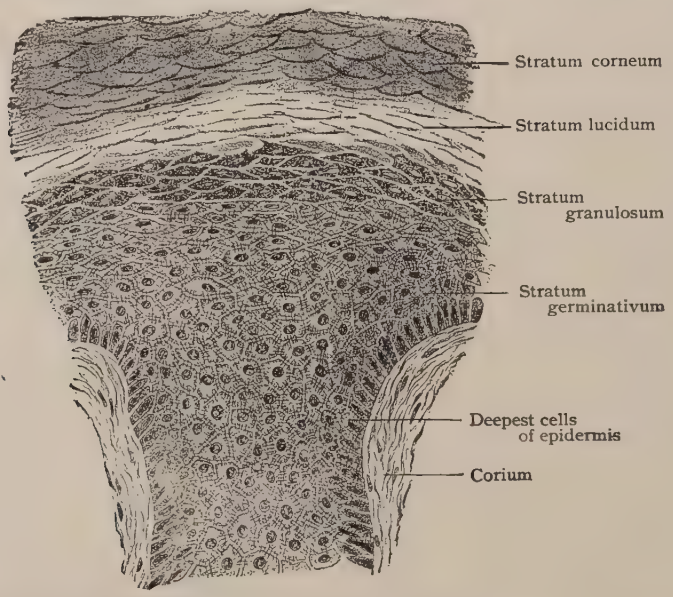


FIG. 360—Portion of preceding section, showing layers of epidermis in more detail; only the deeper part of the epidermis is represented. × 280.

sometimes applied to the deepest layer of the epidermis. As in other epithelia of the stratified squamous type, the deepest cells are columnar and lie with their long axes perpendicular to the supporting connective tissue. The basal ends of the columnar cells are often slightly serrated and fit into corresponding indentations of the corium. Succeeding the single row of columnar elements, the cells of the stratum germinativum assume a pronounced polygonal form, but become somewhat flattened as they approach the stratum granulosum. The number of layers included in the germinal stratum is not only uncertain, but varies with the relation to the papillæ, being greater between than over these projections. The finely granular cytoplasm of the cells of the stratum germinativum shows in thin sections of preserved material delicate **fibrillæ,** which radiate from the nucleus towards the periphery. The fibrillæ are not confined to the cells, but extend beyond and

pass across the intercellular clefts as delicate lines. Microdissection of the living cells affords no evidence for the existence of these intracellular fibres (Chambers and Rényi, '25).

The **stratum granulosum** is exceptionally well marked on the palms and soles and in these localities includes from two to four rows of polygonal cells, that stand out conspicuously in stained sections by reason of the intensely stained particles of **keratohyalin** within their cytoplasm. It is probable that keratohyalin is in some way derived from disintegration of the cytoplasm and represents an initial stage in the process ending in cornification of the succeeding layers of the cuticle.

The **stratum lucidum,** usually wanting in other localities, in the palm and sole appears as a thin almost homogeneous layer, separating the cor-

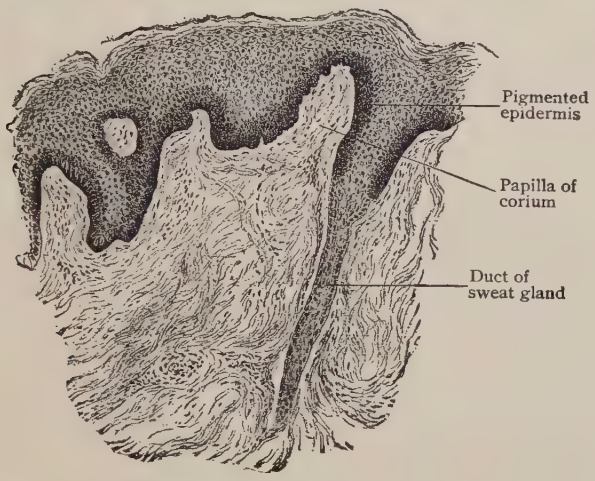


FIG. 361—Section of skin surrounding anus, showing pigmentation of deep layers of the epidermis. × 50.

neous from the granular layer. With the latter it constitutes the stratum intermedium. As indicated by its name, the stratum lucidum appears clear and without distinct cell-boundaries, although suggestions of these, as well as of the nuclei of the component elements, are usually distinguishable. The cells of the stratum lucidum contain a substance, **eleidin,** derived from the keratohyaline particles, which soften and coalesce into a homogeneous semi-fluid material that fills the cells.

The **stratum corneum** includes the remainder of the epidermis and consists of many layers of horny epithelial cells, that contain **pareleidin** and form the exterior of the skin. Where no stratum lucidum exists, as is usually the case, the corneous layer rests upon the stratum granulosum, from which its horny elements are being continually recruited. During their migration towards the free surface, the cells lose their vitality and moisture and become more flattened, until the most superficial ones are converted into the dead horny scales that are being constantly displaced by abrasion.

The **pigmentation** of the skin, which even in white races is conspicuous in certain regions, as on the external genital organs and around the anus, depends upon the presence of colored particles. These lie chiefly within the epidermis, although, when the dark hue is decided, a few small branched pigmented connective tissue cells may appear within the subjacent corium. The distribution of the pigment particles varies with the intensity of color, in skins of lighter tints being principally limited to the columnar cells next the corium. With increasing color the pigment particles invade the neighboring layers of epithelium until, in the dark skin of the negro, they are found within the cells of the stratum corneum, in diminishing numbers towards the free surface. Even when the cells are dark and densely packed, the colored particles never encroach upon the nuclei, which appear as pigment-free areas. The source of the pigment within the epidermis is disputed. Some assume a transference of the colored particles by means of wandering cells or of the processes of pigmented connective tissue cells that penetrate the cuticle, and others accept an independent origin **in situ** within the epithelial elements. While it is established that at times the connective tissue cells are capable of modifying pigmentation, it is equally certain that the earliest, and probably also later, intracellular pigmentation of the epidermis appears without the assistance of the connective tissue or migratory cells, minute colored particles first becoming evident within the epithelial cytoplasm.

The **blood-vessels** of the skin are confined to the connective tissue portion and never enter the epithelium. The **arteries** are derived either from the trunks of the subjacent layer of special cutaneous branches destined for the integument, or indirectly from muscular vessels. Where the blood-supply is generous, as in the palms and soles and other regions subjected to unusual pressure or exposure, the arteries ascend through the subdermal layer to the deeper surface of the corium where, having subdivided they anastomose to form the **subcutaneous plexus.** From the latter some twigs sink into the subdermal layer and contribute the capillary networks that supply the adipose tissue and the sebaceous glands. Other twigs, more or less numerous, pass outwards through the deeper part of the corium and within the more superficial stratum unite into a second, **subpapillary plexus,** that extends parallel to the free surface and beneath the bases of the papilla. The latter are supplied by the terminal twigs which ascend vertically from the subpapillary network and break up into capillary loops that occupy the papillæ and lie close beneath the epidermis (Fig. 362). The arrangement of the cutaneous **veins,** more complex than that of the arteries includes four plexuses lying at different levels within the corium and extending parallel to the surfaces. The first and most superficial one is formed by the union of the radicles returning the blood from the papillæ. The component veins lie below and parallel to the rows of papillæ and immediately beneath the bases of the latter. At a slightly lower level, in the deeper part of the stratum papillare, the venous channels proceeding from the subpapillary network join to form a second plexus. A third occurs about the middle of the corium, while the fourth shares the position of the

subcutaneous arterial plexus at the junction of the corium and subdermal strata. The deepest plexus receives many of the radicles returning the blood from the fat and the sweat-glands, the remainder being tributary to the veins accompanying the larger arteries as they traverse the tela subcutanea.

The **lymphatics** of the skin are well represented by a close **superficial plexus** within the papillary stratum of the corium into which the terminal lymph-radicles of the papillæ empty. The relation of these channels to the interfascicular connective tissue spaces is one only of indirect communication, since the lymphatics are provided with fairly complete endothelial walls. It is probable that the lymph-paths within the papillæ are closely related to the intercellular clefts of the epidermis. Migratory leucocytes often find their way into the cuticle where they then appear as the irregularly stellate **cells of Langerhans** seen between the epithelial elements. A wide-meshed **deep plexus** of lymphatics is formed within the subdermal layer, from which the larger lymph-trunks pass along with the subcutaneous blood-vessels.

The numerous **nerves** within the highly sensitive integument are chiefly the peripheral processes of sensory neurones which terminate in free arborizations between the epithelial elements of the cuticle, or in relation with special endings located, for the most part, within the corium or subdermal connective tissue. Some sympathetic fibres, however, are present to supply the tracts of involuntary muscle that occur within the walls of the blood-vessels or in association with the hairs and the sweat-glands.

FIG. 362—Section of injected skin, showing general arrangement of the blood-vessels; the terminal loops occupy the papillæ. × 30.

On entering the skin the myelinated nerves traverse the subdermal layer, to which they give off twigs in their ascent, and, passing into the corium, within the papillary stratum divide into a number of branches. Those destined for the epidermis beneath the latter break up into many fibres which, losing their medullary substance, enter the cuticle and end in ramifications between the epithelial cells as far as the outer limits of the stratum germinativum. The ultimate endings of the fibrillæ, whether tapering or slightly knotted always occupy the intercellular channels and are

never directly connected with the substance of the epithelial elements. Special **tactile cells** occur in the human epidermis, particularly over the abdomen and the thighs. They are spherical or pyriform and occupy the deeper layers of the cuticle; on the side directed towards the corium, they are in contact with the end-plate, or meniscus, of the nerve. The nerve-fibres particularly concerned with the sense of touch terminate within the connective tissue portion of the skin in special **end-organs.** The structure of these end-organs having been described already, only their chief locations will be noted here.

Meissner's corpuscles (Fig. 117) are especially numerous in the tactile cushions on the flexor surfaces of the hands and feet and are most abundant in those on the volar surface of the distal phalanges, where they approximate twenty to the square millimeter (Meissner). Their favorite situation is the apex of the papillæ, where they appear as elongated elliptical bodies, sometimes in pairs, whose outer pole lies immediately below the epidermis. These corpuscles are additionally, although sparingly, distributed on the dorsum of the hand, the flexor surface of the forearm, the lips, and eyelids, the nipple, and the external genital organs.

The **Vater-Pacinian corpuscles** (Fig. 122) are well represented in the hands and feet and usually occupy the subdermal tissue, although sometimes found within the corium. Their distribution corresponds closely to that of Meissner's corpuscles, being most generous beneath the tactile cushions.

The **Golgi-Mazzoni corpuscles** are modifications of the Pacinian bodies and, like the latter, are found within the subdermal tissue.

The **end-bulbs of Krause** (Fig. 118) occur within the corium, either slightly below or within the papillæ, on the lips and external genital organs, as well as probably in other regions.

The **genital corpuscles** (Fig. 119) lie within the corium of the modified skin covering the glans penis, the prepuce, the clitoris, and surrounding parts of the nymphæ.

The **end-organs of Ruffini** resemble the sensory terminations in tendons and lie within the deeper parts of the corium, often associated with the Pacinian bodies.

The mode of ending of the nerves supplying the hairs and the sweat-gland will be described later in connection with those structures.

THE HAIRS

The appendages of the skin—the hairs, nails, and cutaneous glands—are all specializations of the epidermis; they are, therefore, exclusively of ectodermic origin.

The **hairs** are present over almost the entire body, the few localities in which they are absent being the flexor surface of the hands and feet, the extensor aspect of the terminal segment of the fingers and toes, the inner surface of the prepuce and of the nymphæ and the glans penis and clitoridis. With the exception of those regions in which the growth is sufficiently long to constitute a complete covering, the hairs are for the most part short and

scattered, although subject to great individual variation. The closest set hairs are on the scalp, on the top of the head numbering from 300–320, and in the occipital and frontal regions from 200–240 per square centimeter. On the chin they number about 45, on the mons pubis 35, on the extensor surface of the forearm 24, and on the back of the hand 18 for like areas. Even where their distribution is seemingly uniform, close inspection shows the hairs to be arranged in groups of from two to five.

In their **thickness** the hairs show much variation, not only in different races, individuals, and regions, but also in the same person and part of the body, as on the scalp where fine and coarse hairs may lie side by side. The thickest scalp-hairs have a diameter of 162 μ and the finest one of 10 μ

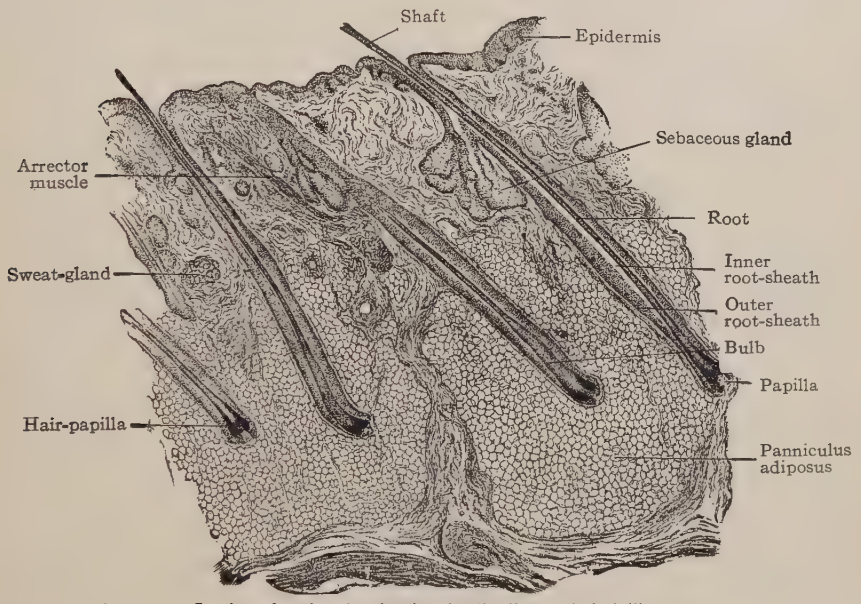


FIG. 363—Section of scalp, showing longitudinally cut hair-follicles. ×14.

with all intermediate sizes. The hairs of the beard vary from 100–200 μ, and those on the pubes from 50–135 μ. In a general way, hairs of light color are finer than dark ones. On attaining their full growth without mutilation hairs do not possess a uniform thickness throughout their length, since they diminish not only towards the tip, where the shaft ends in a point, but also towards the root. This feature is most evident in short hairs, as in those of the eyebrows. The straight and curly varieties of hair depend chiefly upon differences in the curvature of the follicle and the form of the hair. In the case of straight hairs the follicle is unbent and the shaft is cylindrical, and therefore circular in cross-section; hairs that are wavy or curly spring from follicles more or less bent and these hairs are flattened or grooved, with corresponding oval, reniform, or irregularly triangular outlines when transversely cut.

Each hair consists of two parts, the **shaft,** which projects beyond the surface and the **root,** which lies embedded obliquely within the skin, the deepest part of the root expanding into a club-shaped thickening known as the **bulb.** The root is covered with a double investment of epithelial cells, the inner and outer **root-sheaths,** which, in turn, are surrounded by a connective tissue envelope, the **theca.** The entire sac-like structure, consisting of the hair-root and its coverings, constitutes the **hair-follicle.** At the bottom of the latter, immediately beneath the bulb, the wall of the follicle is pushed upwards to give place to a projection of connective tissue, the **hair-papilla,** which carries the capillary loops into close relation with the cells most active in the production of the hair. Save in the case of the finest hairs (lanugo), which are limited to the corium, the hair-follicles traverse the latter and end at varying levels within the fat-laded subdermal layer (panniculus adiposus). In a general way the follicle may be regarded as a narrow tubular invagination of the epidermis, at the bottom of which the hair is implanted and from the entrance of which the shaft projects. The most contracted part of the follicle, the **neck,** lies at the deeper end of the relatively wide funnel-shaped **mouth** of the sac. Closely associated with the hair-follicle, which they often surround, are the **sebaceous glands** that pour their oily secretion at the upper third of the follicle into the space between the shaft and the wall of the sac.

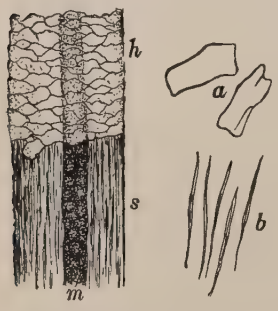


FIG. 364—Portion of shaft of hair; *h*, shaft covered with cuticle; *s*, cortical substance exposed by removal of cuticle; *m*, medulla; *a*, *b*, isolated cells of cuticle and cortical substance respectively. × 240.

The Hair-Shaft.—In many thick hairs, but by no means in all, three parts can be distinguished —the **cuticle,** the **cortex,** and the **medulla.** The latter, however, is usually wanting in hairs of ordinary diameter, being often also absent in those of large size.

The **cuticle** of the hair appears as a transparent outermost layer marked by a network of fine sinuous lines, the irregular meshes of which have their longest diameter placed obliquely transverse. These lines correspond to the free borders of extremely thin, glassy **cuticle-plates** that overlie the hair as tiles on a roof, the imbrication involving from four to six layers. The **cortical substance,** often constituting practically the entire shaft, consists of elongated fusiform cells so compactly arranged that the individual elements are only distinguishable after the action of disassociating reagents. In addition to the remains of the shrunken nuclei, the **hair-spindles,** as these modified epithelial cells are called, possess fibrillæ that pass between adjacent cells similar to the intercellular bridges in the epidermis. A variable amount of **pigment,** either diffuse, or as granules within or between the spindles is a constant constituent of the cortical substance. In blond hair the color is chiefly diffuse, the pigment granules being often entirely wanting; in hair of darker shades, the granules predominate and increase in intensity of color as well as in quantity. As the hair grows outwards from the bulb, it loses much of its moisture, and in consequence later contains

minute air-vesicles that replace the fluid previously occupying the cleft between the hair-spindles.

The **medulla** when well represented, is seen as an axial stripe, somewhat uneven in outline, that varies with illumination, with transmitted light appearing as a dark band and with reflected light as a light one. This peculiarity depends upon the presence of air imprisoned between the shrunken and irregular **medullary cells**—dried and cornified epithelial elements which are connected by branching processes into a network incompletely filling the medulla. The air within the shaft modifies the color of the hair, since its presence tends to lessen the intensity of the tint due to the

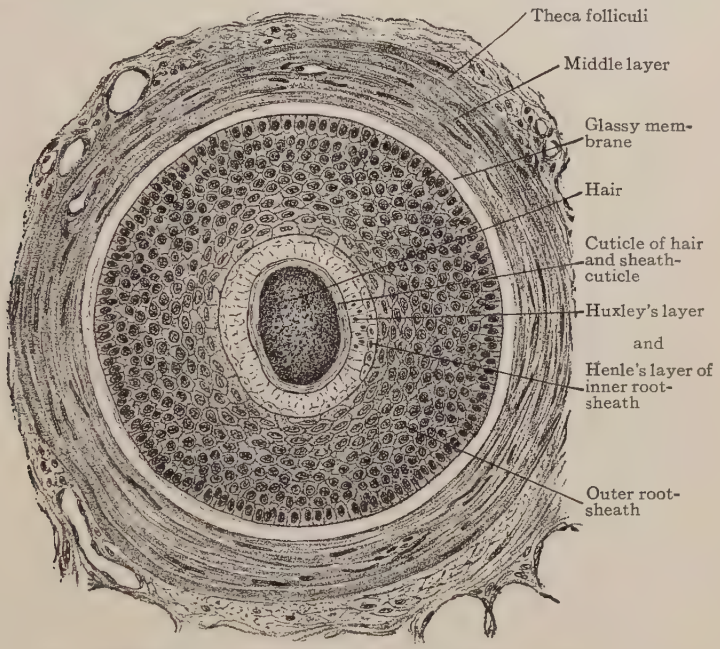


FIG. 365—Hair-follicle cut across about the middle, showing hair surrounded by the root-sheaths. × 285.

pigment. Even when conspicuous, the medulla does not extend the entire length of the hair, often being interrupted and always disappearing before reaching the tip.

The Hair-Follicle.—This structure includes: (1) a connective tissue sheath, the **theca,** contributed by the corium; (2) an epithelial lining, the **outer root-sheath,** continued from the deepest layer of the epidermis; and (3) the **inner root-sheath,** an epithelial investment peculiar to the hair-follicle.

The **theca folliculi** includes three strata: an **outer,** composed of loosely disposed longitudinal bundles of fibrous tissue with a few cells and elastic fibres; a **middle** one, made up of closely placed circular bundles; and a very thin, homogeneous, **inner** coat, the **glassy membrane,** which represents an unusually well developed basement membrane separating corium from cuticle.

The **outer root-sheath** is the continuation of the **stratum germinativum** alone, the other layers of the epidermis thinning out and disappearing before reaching the neck of the follicle. Its cells present the characteristics of those

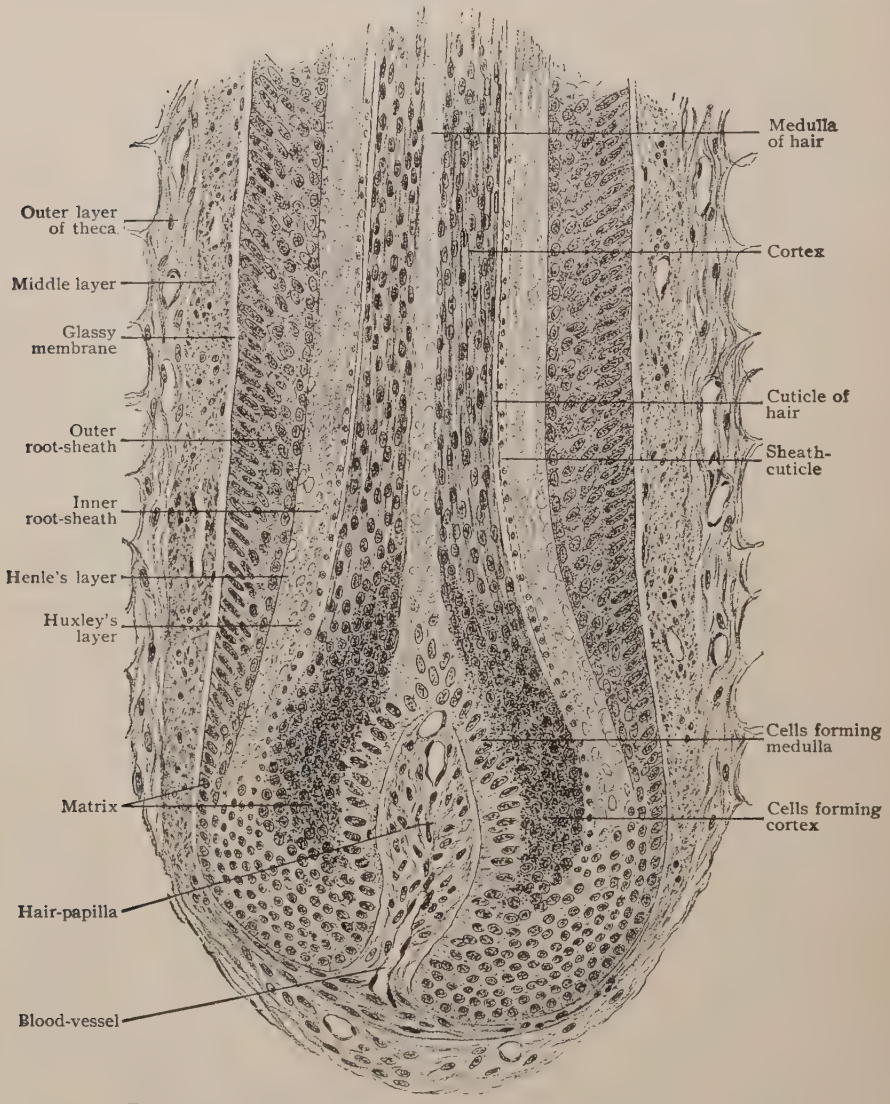


FIG. 366—Longitudinal section through deepest part of hair-follicle. × 285.

of the germinating layer, with exceptionally well marked fibrillæ. On approaching the level of the papilla, the outer root-sheath, which farther above consists of numerous layers, rapidly diminishes in thickness until, on the sides of the papilla, it is reduced to a single row of columnar cells.

The **inner root-sheath,** which is best developed over the middle third

of the hair-root and fades away on reaching the upper third, includes three layers. The outer, known as **Henle's layer,** consists of a single row of flat polygonal cells, often partially separated by oval spaces. Their nuclei are very indistinct or invisible within the cornified cytoplasm. The middle, or **Huxley's layer,** also horny in nature, often comprises only one stratum of nucleated cuboidal cells, but in the thicker hairs two or even three rows of irregularly interlocked cells may be present. The third layer, known as the **sheath-cuticle,** resembles the external coat of the hair, against which it lies, in being extremely thin and composed of flat horny plates. The latter, however, are always nucleated and so disposed that they are opposed to the serrations of the thicker hair-cuticle.

Traced towards the bottom of the follicle, the root-sheaths and the hair which above are sharply defined from one another, become more and more alike until, in the immediate vicinity of the hair-papilla, they blend into a still imperfectly differentiated mass of cells. The deepest elements of this complex, however, are cuboidal or low columnar and form an uninterrupted tract over the papilla, continuous with the outermost cells of the outer root-sheath. It is from the proliferation of these deepest cells that the formative material, or **matrix,** is provided to meet the requirements of growth and replacement of the hairs. Of the three parts of the hair, the medulla is produced by the cells overlying the summit of the papilla, while those converted into the cortical substance, cuticle, and inner root-sheath occupy the sides of the papilla and deepest part of the follicle.

FIG. 367—Section of injected scalp, showing capillary networks surrounding hair-follicles and twigs entering papillæ. × 20.

With few exceptions the hair follicles are associated with two or more **sebaceous glands,** rarely with only one, the ducts of which open into the sac in the vicinity of its neck. The glands usually lie on the side towards which the hair inclines, but sometimes, especially in the case of the smaller hairs, they may completely surround the follicle. Since these glands are outgrowths from the same tissue that lines the follicles, their ducts pierce the outer root-sheath, bringing their oily secretion into direct relation with the hairs.

Most of the larger hair-follicles, particularly those of the scalp, are provided with ribbon-like bundles of involuntary muscle, called the **arrectores pilorum** in recognition of their effect on the hairs. They arise from the superficial part of the corium, pass obliquely downwards to be inserted

into the sheath of the hair-follicle near the junction of corium and subdermal tissue, and on the side corresponding with the inclination of the hair and the situation of the sebaceous glands. Since the latter are closely embraced by the muscular bands, contraction of the muscles exerts pressure upon the glands and facilitates the discharge of their secretion, the **sebum.**

The **blood-vessels** supplying the hair-follicle, which in a sense constitute a special system for each sac, include the capillary loops ascending within the hair-papilla and the network of capillaries surrounding the follicle immediately outside the glassy membrane. The first are derived from a small special twig that ascends to the follicle, and the second from the subpapillary network of the corium. With the exception of those draining the papilla, which are tributary to the deeper stems, the **veins** join the subpapillary plexus.

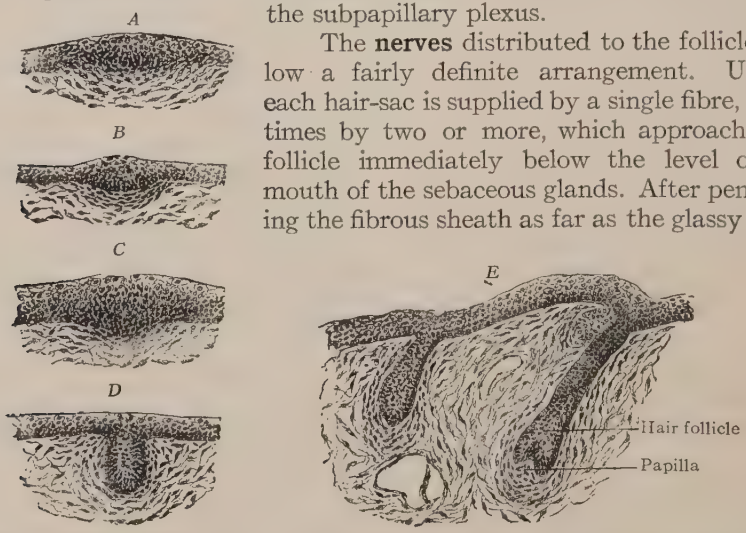


FIG. 368—Sections of developing skin, showing earliest stages in formation of hair-follicle; in *D* epithelial cylinder is invading mesoderm; *E*, later stages of hair-follicles; mesoderm is forming hair-papilla and fibrous sheath of follicle. × 90.

The **nerves** distributed to the follicles follow a fairly definite arrangement. Usually each hair-sac is supplied by a single fibre, sometimes by two or more, which approaches the follicle immediately below the level of the mouth of the sebaceous glands. After penetrating the fibrous sheath as far as the glassy membrane, the nerve-fibre separates into two divisions that encircle more or less completely the follicle and on the opposite side break up into terminal arborizations. The nerve-endings usually lie on the outer surface of the glassy membrane within the middle third of the follicle and only exceptionally are found within the outer root-sheath or the hair-papilla.

Development.—The primary development of the hair begins about the end of the third month of fetal life, as localized proliferations of the epidermis which in section appear as lenticular thickenings. Very soon solid epithelial cylinders sprout from the deeper surface of these areas and invade the subjacent corium to form the rudiments of the **hair-follicles.** The original uniform outline of these processes is early replaced by a flask-shaped contour in consequence of the enlargement of their ends. During their growth the basal ends become concave and the connective tissue which occupies the concavity forms the **hair-papilla.** The embryonal connective

tissue immediately surrounding the epidermal ingrowth differentiates into the fibrous theca and the glassy membrane.

Meanwhile, and even before the formation of the papilla, the epithelial contents of the young follicle differentiate into an axial strand of spindle cells, that later undergoes keratinization and becomes the **hair-shaft,** which grows by subsequent additions from the matrix surrounding the papilla. The peripheral cells of the follicle form the inner and outer root-sheaths. The hair-shaft grows by subsequent additions from the cells of the matrix adjacent to the papilla. These cells are converted into elongated spindles that gradually become horny and assume the characteristics of the cortical substance of the hair. When present, the medulla is developed by the transformation of the cells occupying the summit of the papilla, which enlarge, become less granular, and grow upwards as an axial strand that occupies the centre of the hair and accumulates keratohyalin within its cells. The pigment particles, which appear later, are first evident in the hair-bulb and probably arise within the epithelial tissue. The elements of the hair-cuticle and of the inner root-sheath are differentiated from the matrix-cells at the sides of the papilla. The cells become elongated and converted into the cornified plates of the cuticle both of the hair and of the inner root-sheath. The layers of Huxley and of Henle are derived from cells that soon exhibit granules of keratohyalin, so that on reaching the level of the summit of the papilla the process of cornification has been established.

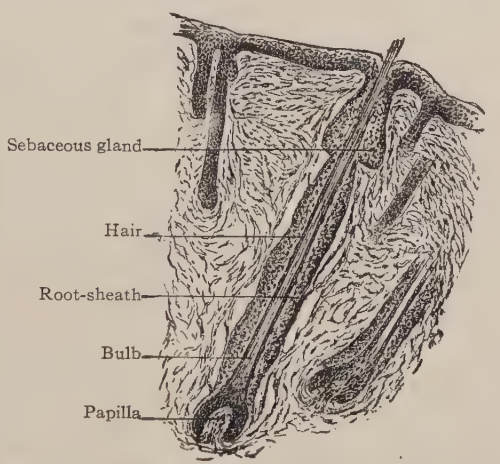


FIG. 369—Later stage of developing follicle; the hair is now differentiated. × 80.

The **growth of the hair** takes place exclusively at the lower end of its bulb, where so long as the hair grows, the conversion of the matrix-cells into the substance of the hair is continuously progressing. By this process the substance already differentiated is pushed upwards by the cells undergoing transformation and these, in turn, are displaced by the succeeding elements. In this way, by the addition of new increments in its bulb, the hair is forced onwards. In the fetus, the first appearance of the hairs is seen on the scalp and regions of the eyebrows about the fifth fetal month and on the extremities about a month later.

The hairs covering the fetus are shed during the last weeks of gestation and immediately followed by birth and replaced by the stronger hairs of childhood. These latter, too, are continually falling out and being renewed until puberty, when in many localities, as on the scalp, face, axillæ and external genital organs, they are gradually replaced by the much longer and thicker hairs that mark the advent of sexual maturity. Even after attaining their mature growth, the individual life of the hairs is limited, those on the

scalp probably retaining their vitality for from two to four years and the eyelashes for only a few months. The **change of hair,** that is continually and insensibly occurring in man, includes the atrophy of the old hair and the development of the new one.

The earliest manifestations of this atrophy are reduction in the size and differentiation of the mass of matrix-cells at the bottom of the follicle and the diminution of the hair-papilla. The progressive reduction of the matrix is accompanied by the production of a club-shaped enlargement of the hair, between which and the shrunken matrix a strand of atrophic epithelial cells for a time remains. With the continued progress of these changes, the root of the **club-hair,** as the degenerating hair is termed, shortens so that the bulbous enlargement recedes from the bottom of the hair-sac until it lies just below the narrow neck of the follicle, where it remains for a longer or shorter period until the hair is dislodged and finally discarded. While the old hair is still lodged in the upper part of the follicle, the first steps towards its replacement are initiated by the stratum germinativum of the old hair-sac, the deepest follicle-cells, contributing by proliferation the material from which the new hair is developed in a manner essentially the same as that by which its predecessor was formed.

THE NAILS

The nails, the horny plates overlying the ends of the dorsal surfaces of the fingers and toes, correspond to the claws and hoofs of other animals and, like them, are composed exclusively of epithelial tissue. The entire nail-plate is divided into the **body,** which includes the exposed portion and the **root** which is embedded beneath the skin in a pocket-like recess, the **nail-groove.** The modified skin supporting the nail-plate, both the body and the root, constitutes the **nail-bed,** the cutaneous fold overlying the nail being the **nail-wall.** During life the nail shows **color-zones,** its projecting portion being immediately followed by a very narrow yellow band that corresponds to the line along which the stratum corneum of the underlying skin meets the under surface of the nail-plate. The succeeding and larger part of the nail is occupied by the broad pink zone which owes its rosy tint to the blending of the color of the blood in the underlying capillaries with that of the horny substance. On the thumb constantly, but on the fingers sometimes only after retraction of the cuticle, is seen a transversely oval white area, the **lunula,** which marks the position of the underlying matrix.

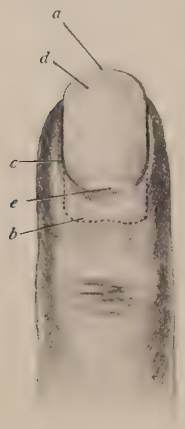


FIG. 370—Part of finger, showing relations of the nail; *a*, *b*, distal and proximal borders of nail; *c*, nail-wall; *d*, line along which epidermis passes to under surface of nail-plate; *e*, lunula.

The substance of the **nail-plate** consists entirely of flattened horny epithelial cells, very firmly united and containing the remains of their shrunken nuclei; hence it is also called **stratum corneum unguis.** These cornified scales are disposed in lamellæ, which, in transverse section, pursue a course in general parallel with the dorsal surface. In nails which possess the longitudinal ridges, however, the latter coincide with an upward arching of the lamellæ dependent upon the conformation of the nail-matrix. In longitudinal section the lamellation is oblique, extending from above downwards and forwards. Minute air-vesicles, imprisoned between the horny

scales, are constant within the nail-substance. When these occur in unusual quantities, they give rise to white spots in the nail.

The **nail-bed** is divided into a proximal, a middle and a distal region, each of which exhibits structural peculiarities and corresponds respectively to the white, rosy, and yellow zone, seen from the dorsal surface of the nail. The most important of these regions is the proximal, known as the **matrix,** which lies beneath the white area and alone is concerned in the production of the nail. So long as the matrix is healthy, it is capable of replacing even an entire lost nail by a new one.

The **corium of the nail-bed** varies in the different regions in the arrangement and size of its elevations. Within the proximal third of the matrix, these elevations occur as low papillæ, which decrease in height and number until they disappear, an even

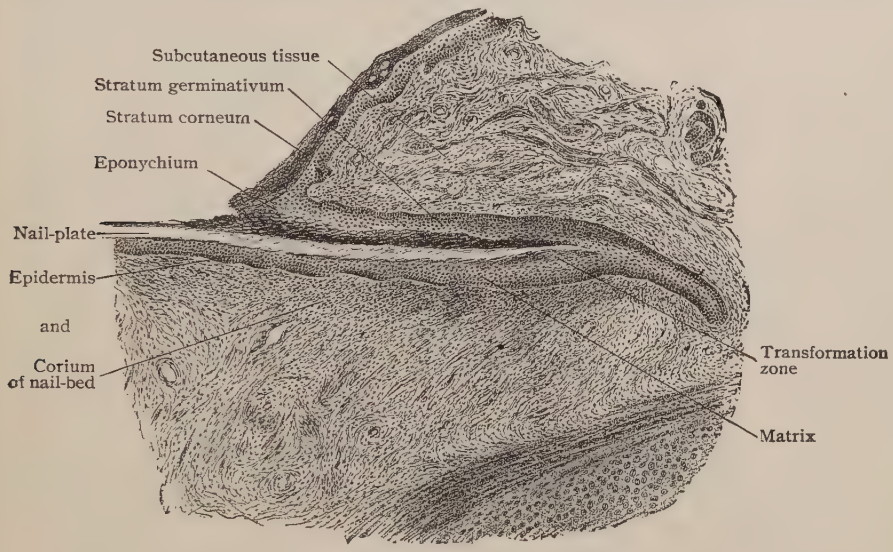


FIG. 371—Longitudinal section of proximal part of nail lying within the nail-groove. × 30.

field occupying the middle of the matrix. This field is succeeded by one possessing closely-set low narrow longitudinal ridges, that at the distal margin of the lunula suddenly give place to more pronounced but less numerous broader lineal elevations. These continue as far as the distal end of the nail-bed and then are replaced by papillæ. Owing to strong fibrous bands and the absence of the usual layer of fatty subdermal tissue, the corium of the nail-bed is closely attached to the bone.

The **epidermis underlying the nail** is of special interest in view of its genetic activity. While the stratum germinativum of the skin covering the finger-tip passes directly and insensibly onto the nail-bed, the entire extent of which it invests (**stratum germinativum unguis**), the stratum corneum ends on reaching the under surface of the nail-plate, the line of apposition corresponding to the narrow yellow zone which defines the distal boundary of the rosy area. Beneath the latter, therefore, the epidermis of the nail-bed consists of the stratum germinativum alone, which, without cornification of any of its cells, rests against the under surface of the nail. Beneath the white zone, that is, within the matrix, the epidermis includes a half-dozen or more layers of the usual elements of the stratum germinativum, surmounted by a like number of strata of cells containing numerous granules of keratohyalin. These granules

impart to this region of the matrix a relative opacity, which contrasts with the more transparent nail-plate, thereby producing the lunula. Since the transformation of the cells of the stratum germinativum into those of the nail-plate is confined to the matrix, it is evident that the continuous growth of the nail takes place along the floor and bottom of the nail-groove, the last formed increment of nail-substance pushing for-

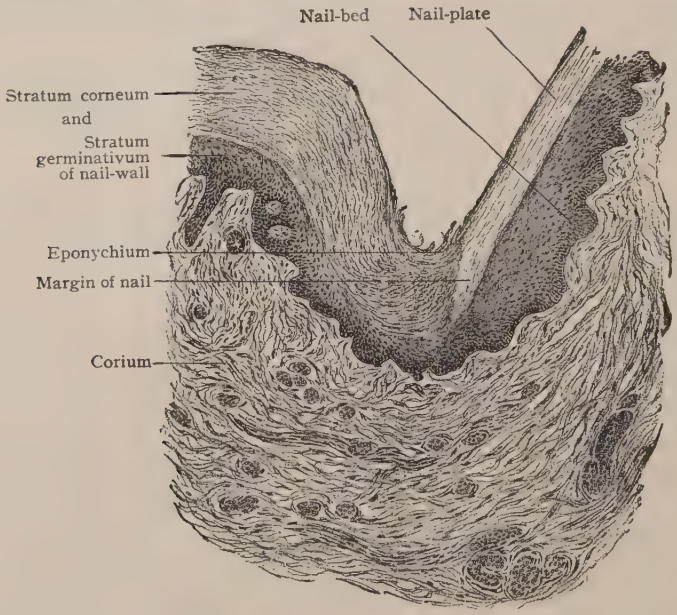


FIG. 372—Section across nail-wall and adjoining part of nail-plate and nail-bed. × 90.

wards the previously differentiated material and thus forcing the nail towards the end of the digit. As the nail leaves the groove, a part of the stratum germinativum of the nail-wall blends with the epidermis and is prolonged for a variable distance over the dorsal surface of the nail-plate as a delicate membranous sheet, the **eponychium,** which usually ends in a ragged and abraded border.

THE CUTANEOUS GLANDS

These structures include two chief varieties, the **sebaceous** and the **sweat-glands,** together with certain modifications, as the ceruminous glands within the external auditory canal, the circumanal glands, the tarsal and ciliary glands within the eyelid, and the mammary glands. In all, the epithelial tissues—the secreting elements and the lining of the ducts—are derivatives of the ectoderm and, therefore, genetically related to the epidermis.

The Sebaceous Glands.—Although these structures, the **glandulæ sebaceæ,** are chiefly associated with the hair-follicles, they also occur, although less frequently independently and in those parts of the skin in which the hairs are wanting, as on the margins of the lip, prepuce, and labia minora. The size of these glands bears no relation to that of the hairs, since among the smallest (.2–.4 mm.) are those of the scalp. The largest (.5–2. mm.) are found on the mons pubis, scrotum, external ear, and nose. Conspicuous

aggregations, modified in form, occur in the eyelids as the tarsal, or Meibomian, glands.

The smallest sebaceous glands are each little more than tubular diverti-

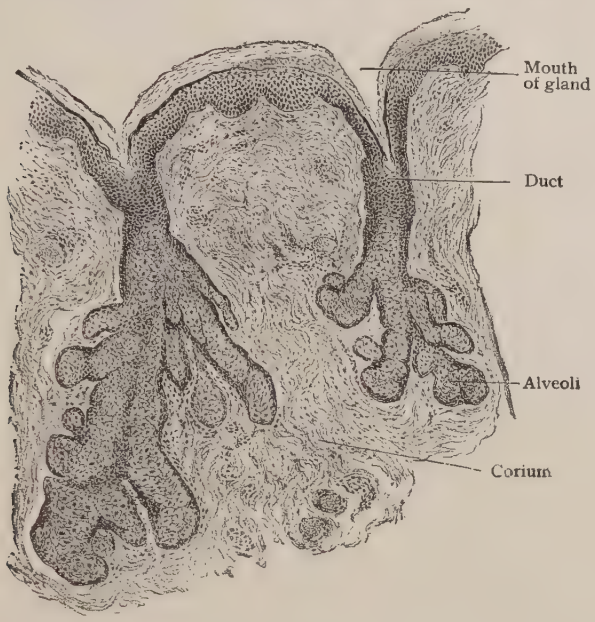


FIG. 373—Sebaceous glands in skin covering ala of nose. × 60.

cula, dilated at the closed ends. In those of the larger size, the relatively short duct subdivides into several expanded compartments, which, in the largest glands, may be replaced by groups of irregular alveoli, with uncertain ducts that converge into a short wide common excretory passage.

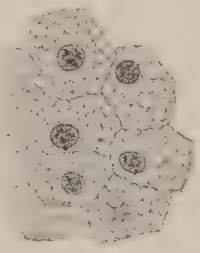


FIG. 374—Cells from alveoli of sebaceous glands, conspicuously showing reticulated cytoplasm. × 650.

The structural components of these glands include a **fibrous envelope,** a **membrana propria,** and the **epithelium,** the first two being continuous with the corresponding coverings of the hair-follicle. The **epithelium** in the ducts and alveoli of the sebaceous glands is directly prolonged from the outer root-sheath of the hair-follicle, where the glands are associated with hair-follicles, or from the epidermis, where the hairs are wanting. The periphery of the alveolus is occupied by a single or incompletely double layer of flattened and imperfectly defined basal cells. These rest immediately upon the membrana propria and are distinguished by their dark cytoplasm and outwardly displaced oval nuclei. Passing towards the centre of the alveolus, the next cells contain a number of small oil-drops which, with each successive row of cells, become larger and appropriate more and more space at the expense of the protoplasmic reticulum in which they are

lodged. In consequence, the cells occupying the centre of an alveolus which is completely filled and without a lumen, contain little more than fat. As the cells are escaping from the glands they lose their nuclei and individual outlines and, finally, are merged as débris into the secretion, or **sebum,** with which the hairs and skin are anointed. The necessity for new cells, created by the continual destruction of the glandular elements that attends the activity of the sebaceous glands, is met by the elements recruited from the proliferating basal cells which in turn pass towards the centre of the alveolus.

The Sweat Glands.—These structures, the **glandulæ sudoriparæ,** occur within the integument of all parts of the body, with the exception of that covering the red margins of the lips, the inner surface of the prepuce, and the glans penis. They are especially numerous in the palms and soles, in the former locality numbering more than 1100 to the square centimeter, and fewest on the back and buttocks, where their number is reduced to about 60 to the square centimeter; their usual quota is between two and three hundred per square centimeter.

Modified simple tubular in type, each gland consists of two chief divisions, the **body** or **gland-coil,** the tortuously wound tube in which secretion takes place, and the **excretory duct,** which opens on the surface of the skin, exceptionally into a hair-follicle, by a minute orifice, the **sweat-pore,** often distinguishable with the unaided eye.

The **body** of the gland, irregularly spherical or flattened, consists of the windings of a single or rarely branched tube. It commonly occupies the deeper part of the corium, but sometimes, as in the palm and scrotum, lies within the subdermal connective tissue. The coiled portion of the gland is not entirely formed by the secretory segment, since, as shown by the reconstructions of Huber, about one fourth is contributed by the convolutions of the first part of the duct.

The secreting portion of the gland-coil, called the **ampulla** on account of its greater diameter, possesses a wall of remarkable structure. The thin **external sheath,** composed of a layer of dense fibrous tissue and elastic fibres supports a well defined **membrana propria.** Immediately within the latter lies a thin but compact layer of **involuntary muscle,** whose longitudinally disposed spindle-shaped elements in cross-section appear as irregularly nucleated cells that encircle the secreting epithelium and displace it from its customary position against the basement membrane. This muscular tissue enjoys the distinction, which it shares with the muscles of the iris, of being developed from the ectoderm. The **secreting cells** constitute a single row of low columnar epithelial elements, that lie internal to the muscle and surround the relatively large lumen. Their finely granular cytoplasm contains a spherical nucleus, situated near the base of the cell, and in certain of the larger glands, as the axillary, includes fat droplets and pigment granules. These are liberated with the secretion of the gland and, when present in unusual quantity, account for the discoloration produced by the perspiration of certain individuals. In the case of the ceruminous glands, the amount of oil and pigment is constantly great and confers the distinguishing characteristics of the ear-wax.

On leaving the gland-coil, the **duct** ascends through the corium with a fairly straight or slightly wavy course as far as the epidermis. On entering the latter its further path is marked by conspicuous corkscrew-like windings, which terminate on the surface by a trumpet-shaped orifice, the **sweat-pore.** In its course through the corium the duct never traverses a papilla or ridge, but always enters the cuticle between the elevations of the corium. On the

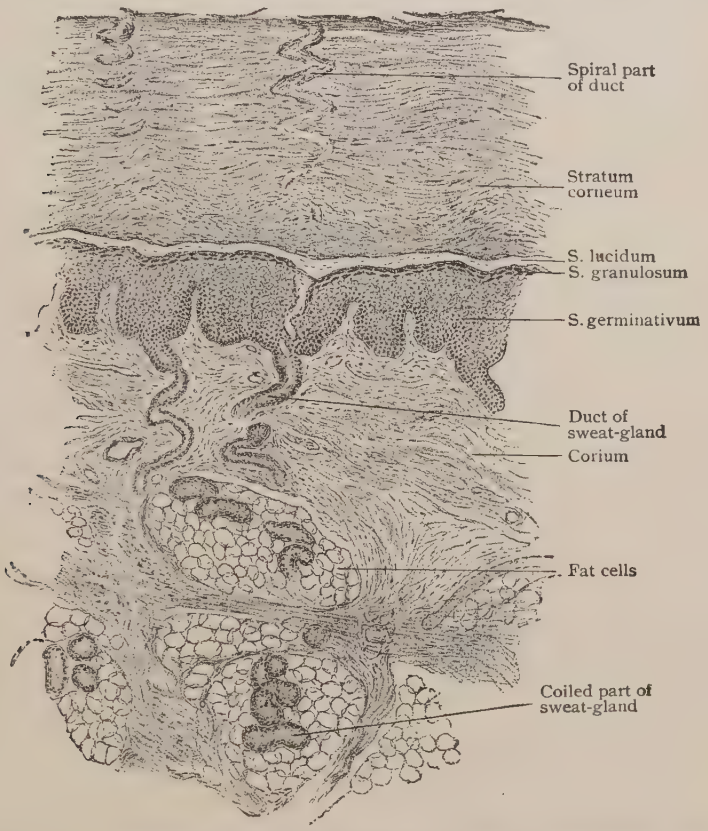


FIG. 375—Section of skin from palm, showing layers of epidermis and parts of sweat-glands extending from surface into tela subcutanea. × 65.

palms and soles, where the pores occupy the summit of the cutaneous ridges, the ducts enter the cuticle between the double rows of papillæ.

The sudden and conspicuous reduction in the size of the tube, which marks the termination of the secreting segment and the beginning of the duct, is accompanied by changes in the structure of its wall. In addition to a reduction of its diameter to one half or less of that of the ampulla, the duct loses the layer of muscle and becomes flattened with corresponding changes in the form of its lumen. The single row of secreting elements is replaced by an irregular double or triple layer of cuboidal cells, which exhibit a homogeneous zone, sometimes described as a cuticle, next the lumen.

On entering the epidermis, the duct not only loses its fibrous sheath and membrana propria, but the epithelial constituents of its wall are soon lost among the cells of the stratum germinativum, so that its lumen is continued to the surface as a spiral cleft bounded only by the cornified cells of the cuticle.

Apart from mere variations in size, certain glands—the **circumanal,** the **ciliary,** and the **ceruminous**—depart sufficiently from the typical form of the coiled glands to entitle them to brief notice. The **circumanal glands,** lodged chiefly within a zone 12–15 mm. wide and about the same distance from the anus, are not all the same, but include, according to Huber, four

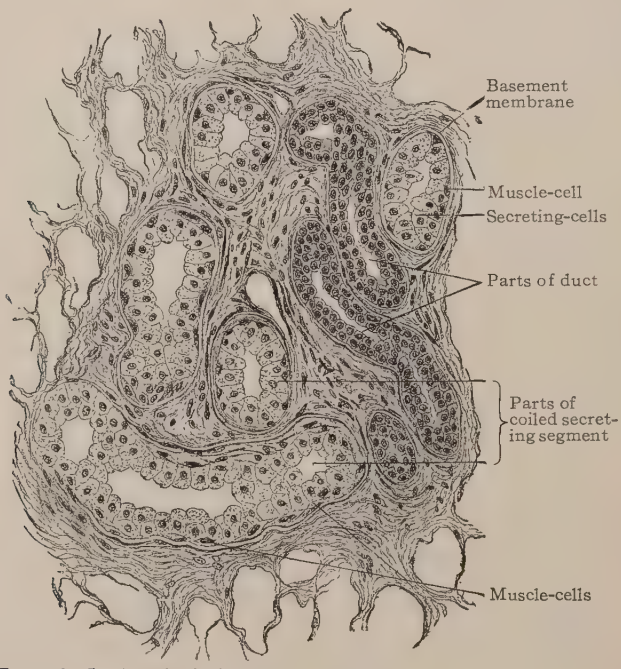


FIG. 376—Section of coiled portion of sweat-gland. × 325.

varieties. In addition to (1) the usual sweat-glands and (2) some (Gay's) of exceptional size, (3) others have relatively straight ducts that end in expanded saccules, from which secondary alveoli arise; finally (4) branched glands of the tubo-alveolar type are present. The **ciliary glands** (Moll's) of the eyelid are not typical coiled structures, but belong to the branched tubo-alveolar groups. The **ceruminous glands,** distinguished by the large amount of oil and pigment mingled with their secretion, are likewise referable to the branched tubo-alveolar type.

The **blood-vessels** of the sweat glands include arterial twigs given off from the cutaneous rete, a capillary network outside the membrana propria, best developed within the coiled portion of the tube, and the veins that join the deeper plexus within the corium.

The **nerves** are especially numerous and consist of unmyelinated sympathetic fibres that traverse the fibrous sheath and form a close epilemmar plexus on the outer surface of the membrana propria. From this network fibrils penetrate the basement membrane and end in close relation with the gland-cells and muscle-elements.

THE EYE

The visual apparatus includes the eyeballs, and their nerve-connections with the primary visual centres in the lateral geniculate bodies and superior colliculi of the mid-brain; and these, in turn, are connected by the optic

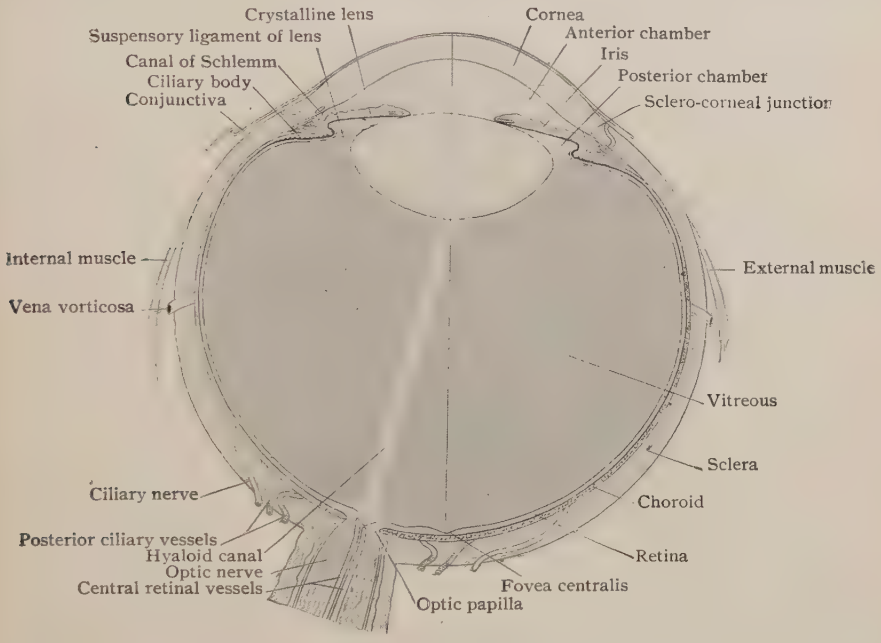


FIG. 377—Diagrammatic horizontal section of right eye. × 2¾.

radiations with the visual cortex of the occipital lobe. With the eyeballs are closely associated other structures, as the eyelids, the lacrimal apparatus, the orbital fascia and fat, and the ocular muscles, which serve for its protection, support, and change of axis.

THE EYEBALL

The human eyeball is an approximate sphere with an antero-posterior diameter of slightly less than one inch (24.2 mm.), and with a slightly shorter vertical diameter (23.2 mm.). The eyeball consists of three concentric tunics, or coats: (1) the **external,** or **fibrous, tunic,** composed of the **sclera** and the **cornea;** (2) the **middle,** or **vascular, tunic,** which is pigmented,

partly muscular and composed, from behind forwards, of the **choroid,** the **ciliary body,** and the **iris;** and (3) the **inner,** or **nervous, tunic,** usually called the **retina,** which is an expansion from the brain and contains the nerve-cells, the nerve-fibres, and the special neuro-epithelium for the reception of the visual stimuli. Within these tunics are enclosed the refracting media—the **aqueous humor,** the **crystalline lens,** and the **vitreous body.**

The Fibrous Tunic

The Sclera.—The sclera, or **sclerotic coat,** is a firm, dense fibrous tunic which forms the posterior five-sixths of the outer coat of the eye, being

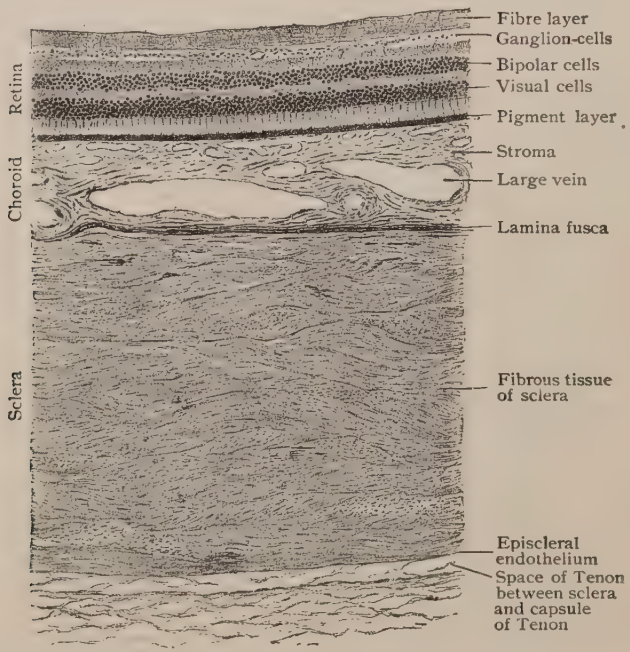


Fig 378—Section through posterior wall of eyeball, showing relative thickness of the fibrous, vascular and nervous coats. × 40.

closely connected with the sheaths of the optic nerve posteriorly, and joining in front with the cornea. In the neighborhood of the optic nerve it measures 1 mm. in thickness, gradually becoming thinner towards the equator, until, just posterior to the attachment of the tendons of the ocular muscles, it measures only .4 mm. After receiving the expansions of these tendons it increases and reaches a thickness of .6 mm. The optic nerve passes through this tunic at a position 1 mm. below and from 2.5–3 mm. to the inner side of the posterior pole of the eye; the outgoing fibres pass between interlacing fibrous bundles, the **lamina cribrosa.** which are intimately associated with the supporting tissue of the nerve.

The sclera is composed of interlacing bundles of white fibrous tissue,

with which is associated a rich network of fine elastic fibres. The clefts between the lamellæ contain irregularly stellate connective tissue cells, the **scleral corpuscles.** On the inner surface of the sclera many of these cells are pigmented and give it a brownish color. Between this layer, the **lamina fusca,** and the underlying choroid is a narrow cleft, the **suprachoroidal space,** both walls of which, together with the fine connective tissue trabeculæ which cross it, are lined with endothelial cells. The outer surface of the sclera, from the optic nerve entrance to the attachment of the ocular muscles, is similarly covered with endothelial plates, and forms part of the lining of Tenon's space. Anterior to the muscle-insertions it is covered with a loose-meshed connective tissue, the **episcleral tissue,** richly supplied with blood-vessels, nerves, and lymph-vessels, and continuous with the subconjunctival tissue of the **conjunctiva scleræ.**

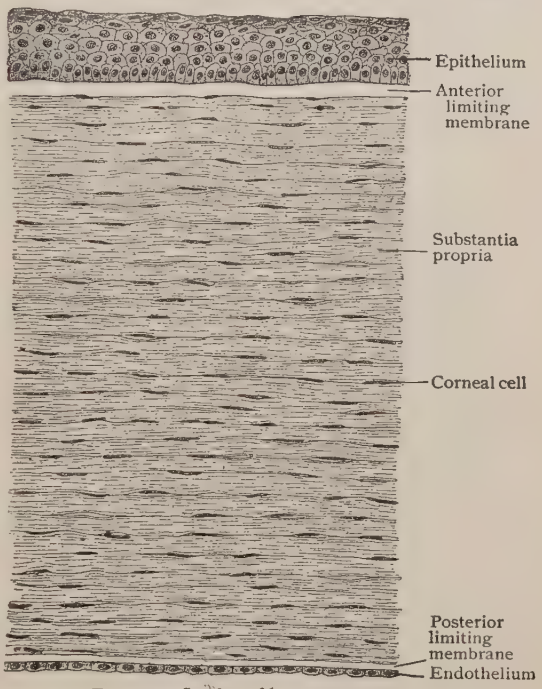


FIG. 379—Section of human cornea. × 85.

The **blood-vessels** of the sclera arise from the arteries which perforate it to supply the vascular coat of the eye. They form a wide-meshed network on the surface of the sclera, which sends anastomosing vessels to a deeper lying set in the scleral substance. In the neighborhood of the optic nerve entrance, the branches of the short posterior ciliary arteries form an arterial circle, which sends branches to the optic nerve and choroid and is, therefore, of great importance in establishing an anastomosis between the choroidal circulation and the **arteria centralis retinæ** which supplies the retina. The **veins** of the sclera empty into the anterior and posterior ciliary veins and into the venæ vorticosæ. At the junction of the cornea and sclera is an important circular venous channel, the **canal of Schlemm,** which will be described later.

The Cornea.—The cornea forms the anterior one-fifth of the fibrous tunic of the eyeball, and, although composed, like the sclera, of bundles of connective tissue, is transparent and allows rays of light to enter the eyeball.

The cornea is composed of five distinct layers, which from without in are: (1) the **anterior epithelium,** (2) the **anterior limiting membrane,** (3) the **substantia propria,** (4) the **posterior limiting membrane,** and (5) the **endothelium.**

The **anterior epithelium** of the cornea is continuous with that covering the surface of the adjacent scleral conjunctiva. It is of the stratified squamous variety, usually five cells deep in man, and measures 45 μ in thickness at the centre, and 80 μ at the periphery. The deepest cells are columnar in form while the middle layers are composed of irregular polyhedral cells, possessed of fine protoplasmic intercellular processes. The superficial layers consist of flattened cells which lie parallel to the free surface and contain nuclei.

The **anterior limiting membrane,** or **Bowman's membrane,** is situated immediately below the epithelium and appears as a homogeneous band, about 20 μ in thickness at the centre and thinner at the periphery, where it terminates without extending into the conjunctiva of the sclera. The membrane may be resolved into fine fibrillæ by suitable reagents, is connected firmly with the underlying connective tissue and is to be considered a special condensation of the latter. It contains no elastic tissue.

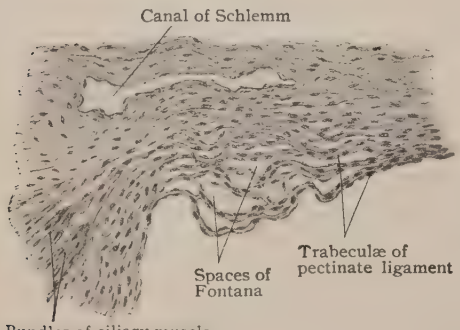


FIG. 380—Section through margin of anterior chamber, showing spaces of Fontana, between the relaxed trabeculæ of the pectinate ligament, and the canal of Schlemm. × 65.

The **substantia propria** constitutes the main portion of the cornea and is made up of interlacing bundles of fibrous connective tissue, directly continuous with those of the adjacent sclera. The bundles are composed of fine fibrillæ, have a flattened form, and are so disposed as to produce regular lamellæ, about sixty in number, running parallel with the surface. The alternating lamellæ have a direction approximately at right angles to each other. Between the fibrillæ and bundles are the cellular elements, the **corneal corpuscles.** These are flattened connective tissue cells, with faintly granular cytoplasm, whose nuclei are irregular and show nucleoli. The cells are provided with branching processes which reach out towards those of other cells, both on the same and adjacent levels. They occupy a system of intercommunicating clefts, the **corneal spaces,** which during life they fill completely, except for the tissue-juices on which their nutrition depends. Occasional leucocytes or wandering cells are found between the fibrous bundles.

The **posterior limiting membrane,** also known as **Descemet's membrane,** or the **posterior elastic membrane,** is a homogeneous band, which varies in thickness from 6 μ at the centre to 12 μ at the periphery. It is less firmly united to the substantia propria than is the anterior limiting membrane, and is less easily affected by acids, alkalies, boiling water, and other reagents. It resembles elastic tissue and is very firm and resistent to injury or perforation from inflammation. At the periphery the membrane splits up into bundles of fine fibres, which are gradually strengthened into a series of firm connective tissue trabeculæ. These fibres are known as the

ligamentum pectinatum iridis and mark the lateral limit of the anterior chamber. They are incompletely covered with endothelial cells and enclose the **spaces of Fontana.** These spaces, better developed in lower mammals than in man, indirectly communicate with the aqueous chamber, and thus form an important region for filtration of fluid from the interior of the eye, by way of the canal of Schlemm, into the anterior ciliary veins.

The **endothelium** covers the free inner surface of the posterior limiting membrane. It consists of a single layer of flat polygonal cells, whose nuclei often extend above the level of the cell-body. The cells are continuous with the cells lining the spaces of Fontana and the anterior surface of the iris.

The **blood-vessels** of the normal cornea are limited to a peripheral zone, from 1–2 mm. in width, in which the terminal twigs of the episcleral arteries end in loops. The remainder of the cornea is free from blood-vessels. The nerves of the cornea are exceedingly numerous. They are branches of the long and short ciliary nerves, from 40 to 45 in number, and form an **annular plexus** that surrounds the margin of the cornea. Entering the latter, they form a number of plexuses within the corneal stroma at various depths.

The Vascular Tunic

The middle, or vascular, coat, sometimes called the **uveal tract,** consists of a connective tissue sheath supporting blood-vessels, and lies internal to the outer fibrous tunic. It extends from the entrance of the optic nerve to the pupil and includes three portions, which from behind forward are: the **choroid,** the **ciliary body,** and the **iris.** The choroid and ciliary body are in contact with the sclera, but the iris bends sharply inwards and floats in the aqueous humor, incompletely dividing the space anterior to the crystalline lens into the posterior and the anterior chamber.

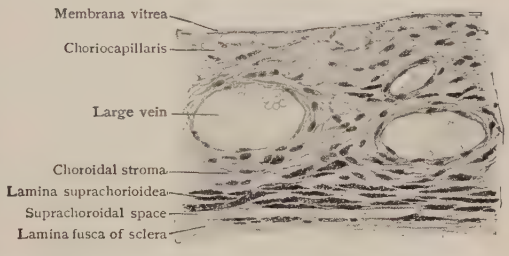


FIG. 381—Section of choroid, showing capillary layer and large vessels. × 200.

The Choroid.—The choroid contributes the posterior two-thirds of the vascular coat. It lies between the sclera and the retina and extends from the optic nerve entrance to the anterior limit of the visual part of the retina at the ora serrata, its main function being to supply nutrition to the nervous tunic. It is a delicate coat, with a thickness of .2 mm. near the nerve and about half as much at the ora serrata. The **outer surface** is roughened by the trabeculæ of connective tissue which cross the suprachoroidal space and connect the choroid with the overlying sclera. Its **inner surface** is smooth and covered by the pigmented cells of the retina, which are so closely attached that they frequently adhere to the choroid when the membranes are separated.

The choroid consists of four layers, which from without inwards, are:

(1) the **lamina suprachorioidea,** (2) the **choroid proper,** which contains the larger vessels, (3) the **choriocapillaris,** or layer of fine capillaries, and (4) the **membrana vitrea.**

The **lamina suprachorioidea** is the outer boundary of the choroid and connects it with the sclera. It is composed of interlacing bundles of fibrous tissue, which are strengthened by rich networks of elastic fibres. The cellular elements consist of (**a**) flattened endothelial plates, which line the tissue-clefts and cover the connective tissue trabeculæ connecting the choroid and the sclera; and (**b**) large irregularly branched connective tissue cells, the

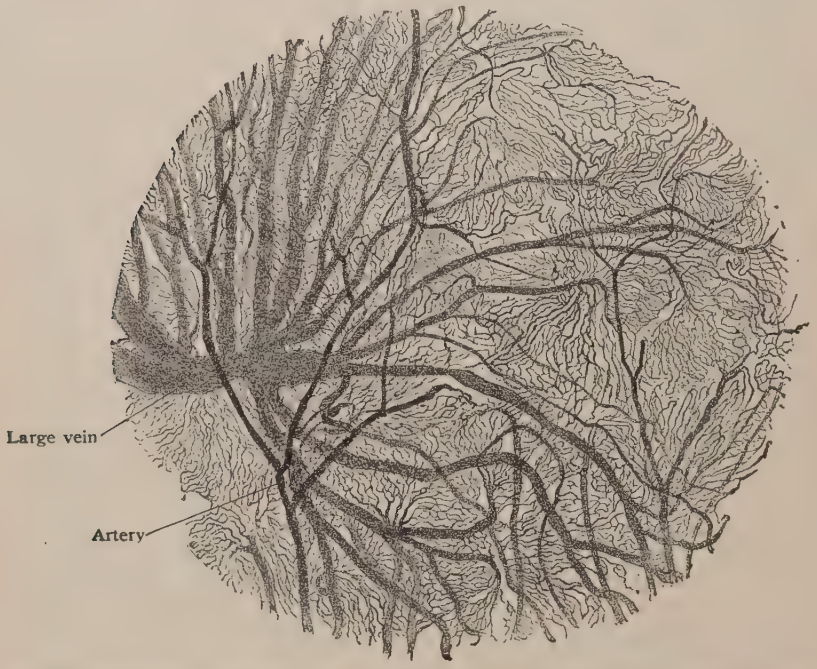


FIG. 382—Surface view of injected human choroid, showing venous radicles converging to form large vein. × 18

chromatophores, which are conspicuous on account of their deep pigmentation. The lamellæ of the suprachoroid continue, without definite boundary, into the subjacent choroidal stroma.

The **choroid proper,** as the choroidal stroma is called, has the same general structure as the suprachoroidal layer, but the connective tissue elements are denser and support a **large number of blood-vessels,** between which are placed the stellate chromatophores. The largest vessels occupy the outer part of the coat and are chiefly venous. They are surrounded with perivascular lymph-sheaths and converge in peculiar whorls to form four or five large trunks, the **venæ vorticosæ**, which pierce the sclera in the equatorial region and drain not only the choroid but partly also the ciliary body and iris. The arteries, derived from the short ciliary vessels, lie

internal to the veins. Their walls contain longitudinally disposed muscle-fibres in addition to the customary circular ones.

The **choriocapillaris,** or membrane of Ruysch, is composed of capillaries which form an extremely close meshwork, embedded within a homogeneous non-pigmented matrix. Between the choriocapillaris and the layer of larger vessels is a narrow boundary zone of closely woven fibro-elastic strands, which is nearly free from pigment. In some animals this layer possesses a peculiar metallic reflex and is known as the **tapetum fibrosum;** in carnivora its iridescent appearance is due to the presence of cells containing minute crystals (**tapetum cellulosum**).

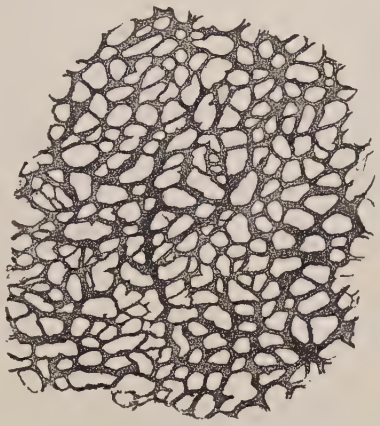


Fig. 383—Portion of injected choroid, showing surface view of choriocapillaris layer. × 130.

The **membrana vitrea,** or membrane of Bruch, the innermost layer of the choroid, measures only 2 μ in thickness. It separates the choriocapillaris from the retina. The **nerves** of the choroid form a plexus within the lamina suprachorioidea, which contains groups of ganglion-cells and sends numerous unmyelinated fibres chiefly to the muscular coats of the arteries.

The Ciliary Body.—The ciliary body, the middle portion of the vascular tunic, extends from the ora serrata to the sclero-corneal junction.

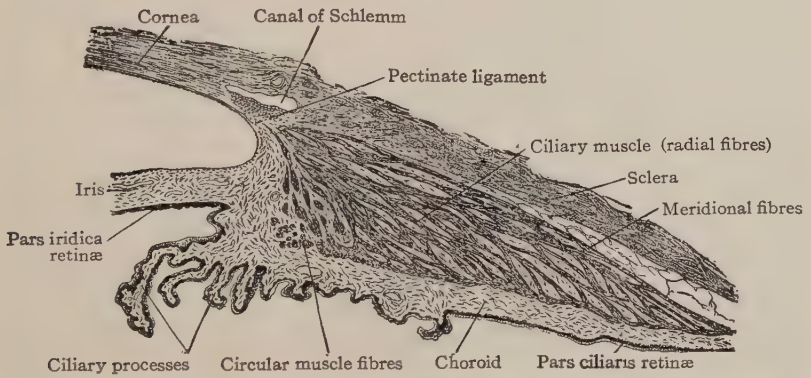


Fig. 384—Meridional section of ciliary region, showing ciliary body with its muscle and processes. × 40.

Sections through the eyeball in a meridional direction (Fig. 384) show a triangular form. The outer side adjoins the sclera, the inner is covered by the thin pigmented extension of the retina, and the short anterior side, at right angles to the outer, extends inwards from the pectinate ligament towards the lens. The ciliary body presents three subdivisions: the **ciliary ring,** the **ciliary processes,** and the **ciliary muscle.**

The **ciliary ring** (**orbiculus ciliaris, pars plana**), consists of a smooth band of tissue, 4 mm. in width, in advance of the ora serrata. It differs in structure from the choroid in the absence of the choriocapillaris, its vessel running in a longitudinal direction and returning the blood from the iris and ciliary body to the venæ vorticosæ. On its inner surface, delicate meridionally placed folds make their appearance, by the union of which the ciliary processes are formed.

The **ciliary processes** form an annular series of folds, about seventy in number, which surround the lens and act as points of attachment to its suspensory ligament. Commencing by the union of several plications of the orbiculus ciliaris, they rapidly increase in height and breadth, until they reach an elevation of from .6–.8 mm., and then fall suddenly to the iris-level. The distance from the margin of the ciliary ring to the root of the iris is about 2.5 mm. The ciliary processes consist of a rich network of vessels embedded in a pigmented connective tissue stroma, like that of the choroid. The inner surface is covered with the double layer of cells representing the ciliary portion of the retina (**pars ciliaris retinæ**). The layer of cells adjoining the stroma is deeply pigmented but the superficial layer is made up of clear cells, which are concerned in the formation of the aqueous humor. On the volume of the latter depends the intra-ocular pressure. This varies to some extent with the blood pressure.

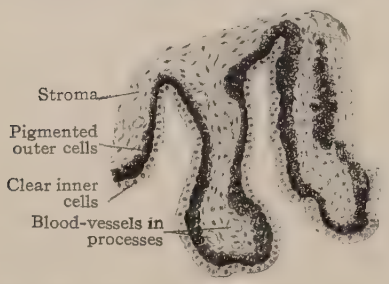


FIG. 385.—Section of ciliary processes, showing layers of ciliary part of nervous tunic. × 80.

The **ciliary muscle** occupies the outer portion of the ciliary body lying between the sclera and the ciliary processes. It forms an annular band of involuntary muscle, which in meridional sections has a triangular form. Its main fibres arise from the sclera and pectinate ligament, at the sclero-corneal junction internal to the canal of Schlemm, and run in a **meridional** direction backwards along the sclera to be inserted into the choroidal stroma. The inner angle of the triangle, at the base of the iris, is occupied by a band of **circularly** disposed fibres, the **circular ciliary muscle of Müller.** Between the circular and meridional portions, the fibres have a **radial** arrangement. Acting from its origin, the ciliary muscle draws forward the ciliary processes and relaxes the lens-capsule, thus allowing the lens to become more convex. The ciliary muscle is, therefore, the muscle of accommodation, for near and distant vision.

The **blood-vessels** of the ciliary body, from the anterior and the long ciliary arteries form a ring around the root of the iris, the **circulus arteriosus iridis major,** from which vessels are sent inwards to supply the iris, ciliary muscles, and ciliary processes. The **veins** from the ciliary muscle empty chiefly into the anterior ciliary veins; those from the ciliary processes and a few from the ciliary muscle pass backwards and become tributary to the **venæ vorticosæ.** The **nerves** of the ciliary body form an annular plexus within the ciliary muscle and include sensory and

sympathetic fibres, the latter being distributed to the walls of the blood-vessels and to the involuntary muscle.

The Iris.—The iris forms the anterior segment of the vascular tunic

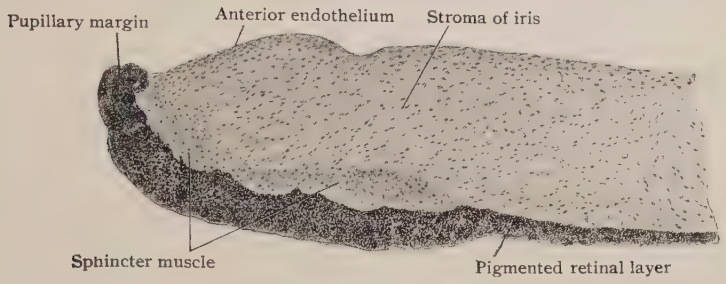


FIG. 386—Section of pupillary end of iris. × 210.

and is visible through the cornea. Slightly to the inner side of its centre is placed an approximately circular opening, the **pupil**, which changes its size with the intensity of the light. The periphery of the iris is attached to the ciliary body behind and receives fibres from the pectinate ligament in front. The color of the iris varies in different individuals and gives the "color of the eye." It is dependent partly upon the amount of pigment within the iris-stroma, and partly upon the density of the pigmentation of the cells on its posterior surface, (pars iridica retinæ). In light blue eyes, the stroma contains almost no pigment and the posterior pigment layer, seen through it, gives a bluish tint; whereas in brown eyes the stroma contains so much pigment that the effect of the posterior pigment layer is augmented and the iris appears brown.

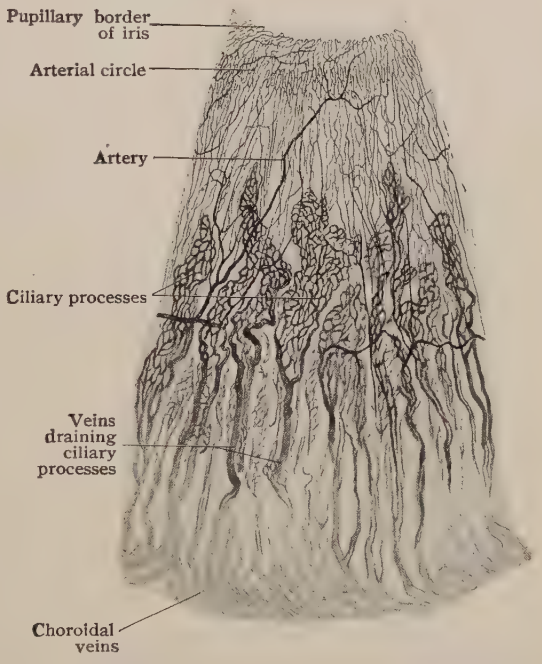


FIG. 387—Injected ciliary processes and iris; posterior surface. × 20.

The **stroma** of the iris encloses numerous thick-walled blood-vessels, radiating from the ciliary border towards the pupil. They are supported by a delicate connective tissue framework, which contains branching pigmented cells, many nerves, and tissue-spaces. The

anterior surface is covered with a single layer of polygonal **endothelial cells,** continuous with those lining the cornea. Beneath these cells is a condensation of the connective tissue stroma, **the anterior boundary layer,** in which the cells are closely placed. Minute clefts in the tissue are said to form communications between the anterior chamber and the interfascicular tissue-clefts. The **muscular tissue** of the iris includes two distinct masses, the sphincter and dilatator of the pupil.

The **sphincter muscle** is a band of involuntary tissue about .7 mm. in width, surrounding the pupil and situated in the vascular stroma, back of the blood-vessels.

The **dilatator muscle** is a sheet of smooth muscle-fibres in the position formerly described as the posterior limiting lamella. Its fibres arise from the anterior layer of cells of the pars iridica retinæ, adjoining the stroma. Both layers of cells are so deeply pigmented that the cells are obscured. The posterior cells are larger polygonal elements which gradually lose their pigment as they approach the ciliary processes. Since the iridical muscles are developed from the cells of the optic cup, they represent muscles of ectodermic origin.

The **blood-vessels** of the iris pass radially inwards from the **circulus arteriosus iridis major** at the periphery. Near the pupillary border, they form a second ring, the **circulus arteriosus iridis minor,** branches from which supply the sphincter muscle and the pupillary zone. The **venous radicles** unite to form trunks which accompany those from the ciliary processes to empty into the **venæ vorticosæ.** The **tissue spaces** are represented by the interfascicular clefts which communicate with the anterior chamber, with the spaces within the ciliary body, and with the spaces of Fontana. The **nerves** of the iris, branches of the ciliary nerves, follow the course of the blood-vessels and, branching, form a plexus of unmyelinated fibres, which supply chiefly the involuntary muscle including that of the vessels.

The Nervous Tunic

The Retina.—The retina, the light-perceiving portion of the eye, represents a modified portion of the brain-wall itself, having developed from an evagination of the early neural tube. In its entirety it extends from the optic nerve entrance to the pupillary border. The functioning portion, or **pars optica retinæ,** reaches as far forwards as an irregular wavy line, the **ora serrata;** anterior to this, the retina is represented by an atrophic portion, consisting of a double layer of cells covering the ciliary body and the iris, respectively the **pars ciliaris retinæ** and the **pars iridica retinæ.** The pars optica retinæ is closely applied to the inner surface of the choroid and is in contact with the hyaloid membrane investing the vitreous body. It gradually diminishes in thickness from .4 mm. at the posterior pole to .1 mm. near the ora serrata. At the posterior pole of the eyeball, 3 mm. to the outer side of the optic nerve entrance, the retina exhibits an oval area, the **yellow spot,** or **macula lutea;** the centre of the latter is marked by a small

depression, the **fovea centralis,** which corresponds to the region of most acute vision.

The retina is composed of nervous elements which are supported by a specialized sustentacular tissue, or neuroglia. Morphologically it must be considered as composed of two lamellæ, which correspond to the outer and

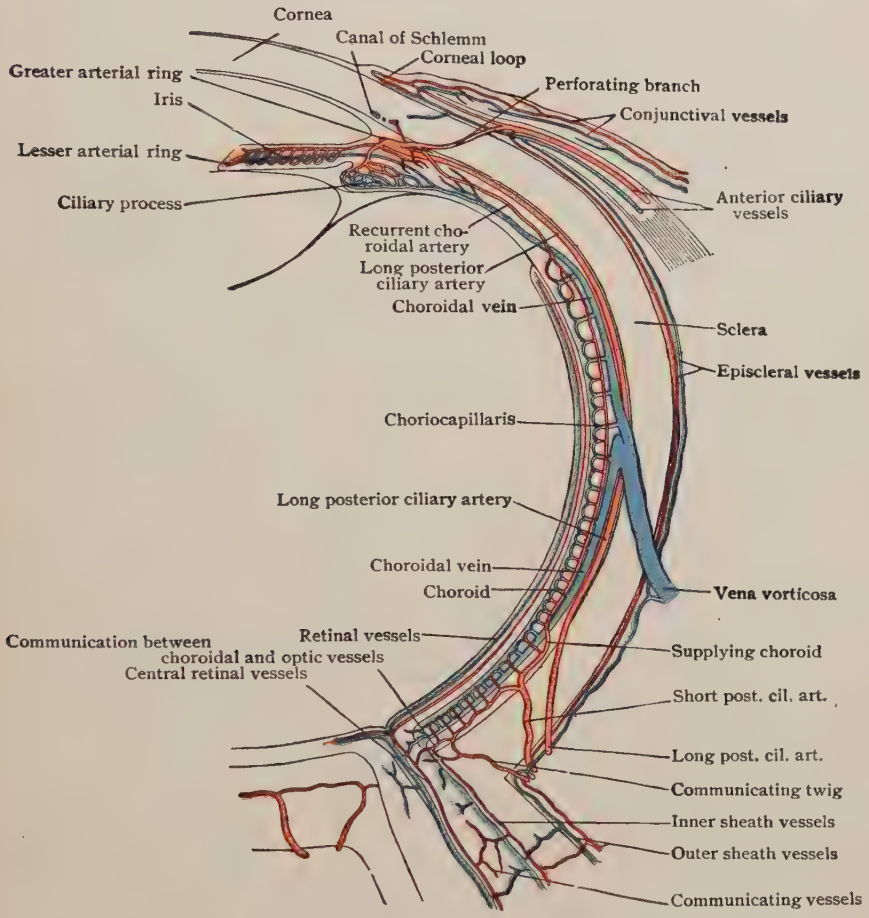


FIG. 388—Diagram illustrating circulation of eyeball. (*Leber.*)

inner walls of the optic cup, the hollow outgrowth of the brain-sac from which it is developed. The fundamental divisions of the retina are: (1) the external lamella, the **pigmented layer** on the outer surface; and (2) the internal lamella, which includes the remaining layers of the retina. The inner lamella may be subdivided further into the **neuro-epithelial** and the **cerebral** layers. Sections of the retina (Fig. 389) show under the microscope from without inwards the following layers:

I. Outer Lamella of Optic Vesicle	1. Pigmented layer, adjoining the choroid coat	Pigmented layer
	2. Layer of rods and cones	Neuro-epithelial layer
	3. Layer of bodies of visual cells, or outer nuclear layer	
II. Inner Lamella of Optic Vesicle	4. Outer plexiform layer	Cerebral layer
	5. Layer of bipolar cells, or inner nuclear layer	
	6. Inner plexiform layer	
	7. Layer of ganglion-cells	
	8. Layer of nerve-fibres	

To these nervous layers must be added two delicate membranes, (1) the **membrana limitans interna,** which bounds the inner surface of the retina, and (2) the **membrana limitans externa,** which lies between the outer nuclear layer and the layer of rods and cones. These membranes represent the terminal portions of the supporting neuroglia fibres, or **fibres of Müller.**

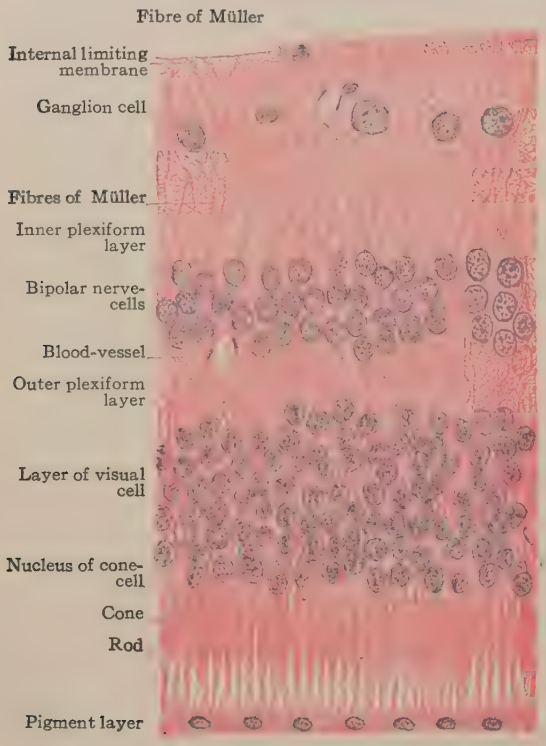


Fig. 389—Section of human retina, near posterior pole of eyeball. × 230.

The **pigmented layer,** formed of deeply pigmented cells, constitutes the most external layer of the retina and represents the outer wall of the fetal optic vesicle. It is composed of a single layer of hexagonal cells, from 12–18 μ in diameter, the protoplasm of which is loaded with fine, needle-shaped crystals of pigment (**fuscin**). The outer portion of the cells is almost free from pigment and contains the nucleus. From the inner border fine protoplasmic processes extend inwards between the rods and cones of the neuro-epithelial layer, and under the influence of light the pigment particles wander into these processes and thus surround the ends of the rods and cones.

The **layer of rods and cones,** although usually described as a distinct stratum, is only the highly specialized outer zone of the layer of visual cells. It is composed, as its name indicates, of two elements, the **rods** and the **cones,** which are the outer ends of the rod- and cone-visual cells. They are closely set, with their long axes perpendicular to the surface of the retina.

The rods far outnumber the cones, except in the fovea centralis, in which location cones alone are found. In the macula each cone is surrounded by a layer of rods; elsewhere the cones are separated by intervals occupied by three or four rods.

The **rods** of the human retina (Fig. 391, B) have an elongated cylindrical form and measure approximately 60 μ in length and 2 μ in diameter. Each rod is composed of an **outer** and an **inner segment,** of about equal length. The outer segment possesses a uniform diameter, is doubly refracting and is the situation of the **visual purple** that tinges the living retina. The inner rod-segment is somewhat thicker and has an ellipsoidal form. It is singly refracting and homogeneous in structure. From its inner extremity extends the delicate **rod-fibre,** or body of the rod-cell, through the external limiting membrane into the outer nuclear layer, where the nucleus of the rod-visual cell is found.

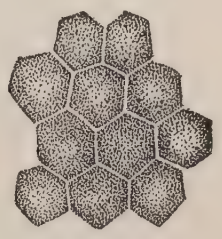


FIG. 390—Pigmented cells from outer layer of retina; surface view. × 350.

The **cone-visual cell** is composed of the same two general divisions as the rod-cell, the specialized outer part, the **cone,** and the body within the external nuclear layer. The cones are shorter than the rods and have a length of 35 μ. Each one (Fig. 391, A) is composed of an outer narrow cone-shaped segment and an inner broader one, which is distinctly ellipsoidal, with a diameter of 7 μ. The inner segment is double the length of the outer and continues as the **cone-fibre** or body of the cone-cell in the outer nuclear layer.

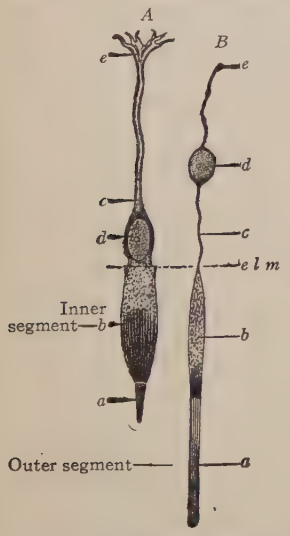


FIG. 391—Visual cells from human retina; *A*, cone-cell, *B*, rod-cell; *a*, *b*, outer and inner segments; *c*, attenuated bodies (fibres), with nucleus (*d*) and central ends (*e*); *e l m*, external limiting membrane. (*Greeff.*)

The **outer nuclear layer,** the inner portion of the neuro-epithelial layer, is about 60 μ thick and composed of the bodies of the rod- and cone-visual cells, which show chiefly as the nuclei. The **rod-nuclei** occupy an elliptical enlargement of the attenuated rod-fibres, and are placed at varying levels within the layer. The rod-fibres are continued as a thin protoplasmic process into the outer reticular layer, where they form small end-knobs which are associated with the outer terminals of the small nerve-cells, the rod-bipolars. The **cone-nuclei** are less numerous than those of the rods, and are found only in the outer portion of the nuclear layer. The cone-fibres are broader than the corresponding parts of the rod-cells and are continued through the outer nuclear layer as far as the outer portion of the external plexiform layer. Here they end with broad bases, from which delicate processes extend inwards to interlace with the terminal arborizations of the cone-bipolars.

The **outer plexiform layer** is a narrow stratum, between the outer and

the inner nuclear layer, and constitutes the first of the cerebral layers of the retina. It is composed of the dendritic arborizations of the bipolar nerve-cells of the succeeding layer, which lie in close relation with the foot-plates of the cone-cells and with the end-knobs of the rod-fibres.

The **inner nuclear layer,** the most complicated of the retinal strata, measures 35 μ in thickness, near the optic disk. It contains nervous elements of three main types—the **bipolar cells,** the **horizontal cells,** and the **amacrine cells.**

The **bipolar cells,** the ganglion-cells of this layer, are of two chief varieties, the **rod-bipolars** and the **cone-bipolars.** They are oval cells, each sending an axone inwards, which ends in relation with the large nerve-cells of the ganglion-cell layer, and a dendrite outwards, which is associated with the visual cells.

The **horizontal cells** have flattened cell-bodies and send out dendrites, which terminate in close association with the bases of the rod- and cone-visual cells. Each horizontal cell possesses also an axone which ends in a richly branched arborization about the visual cells. The horizontal cells probably serve as association fibres between the visual cells.

The **amacrine cells** are placed in the inner portion of the nuclear layer. They possess richly branched dendritic processes which ramify in the inner plexiform layer.

The **inner plexiform layer,** 40 μ thick, appears similar to the corresponding outer zone, and is composed of the interlacing axones of the bipolar, amacrine, and horizontal cells from the inner nuclear layer and the dendrites of the large ganglion-cells in the subjacent retinal layer. Intermingled with these are the fibres of Müller, which show as conspicuous vertical striæ, with lateral offshoots.

The **layer of ganglion-cells** consists, throughout the greater part of the retina, of a single row of large multipolar neurones, each with a cell-body containing a vesicular nucleus and nucleolus and exhibiting typical Nissl bodies and a fibrillar structure. Their axones pass inwards and become the nerve-fibres of the fibre layer. Converging towards the optic entrance, they become consolidated into the optic nerve and continue to the brain. The dendrites of the ganglion-cells, one to three in number, run outwards into the inner plexiform layer and end as richly branched arborizations in connection with the centrally directed processes from the bipolar cells.

The **nerve-fibre layer** is composed almost entirely, but not exclusively, of the axones of the ganglion-cells of the preceding layer. The individual fibres are collected into bundles of varying size, which take a horizontal course and converge towards the optic disk. Within the retina they are normally devoid of myelin sheaths, but acquire them after passing through the lamina cribrosa of the sclera. A few of the fibres are **centrifugal,** arising from ganglion-cells within the brain, and terminate apparently in relation with the amacrines of the inner nuclear layer.

The **sustentacular tissue,** the neuroglia of the retina, exists in two forms—as the **fibres of Müller** and the **spider cells.**

The **fibres of Müller** are modified neuroglia cells, which pass vertically

from the inner surface of the retina through the succeeding layers as far as the bases of the rods and cones (Fig. 392). The inner extremities of the fibres are conical expansions, that by apposition form a continuous sheet, the **membrana limitans interna.** As the fibres traverse the retinal layers, they give off delicate lateral offshoots, which break up into a fine supporting reticulum. Within the inner nuclear layer each fibre presents a broad expansion containing the oval nucleus of the sustentacular cell. After traversing the outer nuclear layer their broadened peripheral ends come into contact and form a perforated sheet, the **membrana limitans externa.** From the latter delicate offshoots continue outwards and embrace the bases of the individual rods and cones. In addition to the robust fibres of Müller, neu-

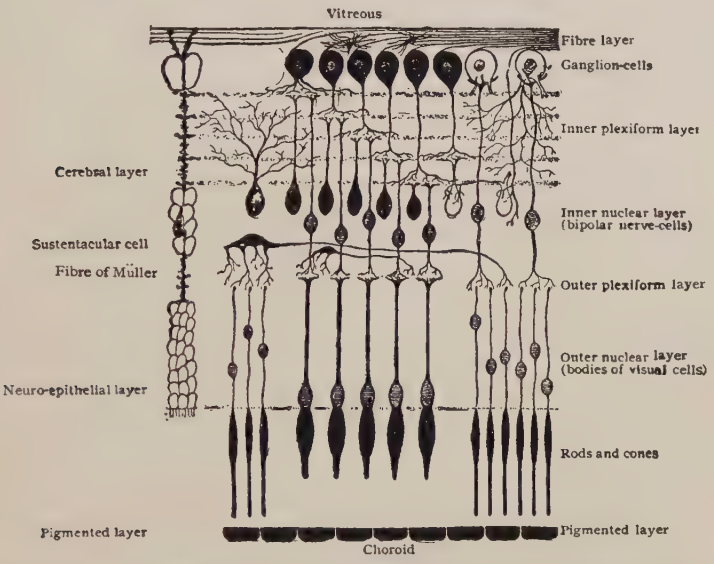


FIG. 392—Diagram illustrating structure of retina and relations of three fundamental layers. (*Greeff.*)

roglia cells, in the form of **spider cells,** are found in the nerve-fibre and ganglion-cell layers.

The Macula Lutea.—The structure of the retina undergoes important modifications in two areas, at the macula lutea and at the ora serrata. In the former the ganglion-cells increase rapidly in number as the macula is reached so that instead of forming a single layer they are distributed in from eight to ten strata. The inner nuclear layer is also increased in thickness. Within the **fovea centralis,** however, in order to reduce to a minimum the layers traversed by the light-rays, the cerebral layers are almost entirely displaced, only the absolutely essential retinal strata—the pigment cells and the visual cells with their necessary connections—being retained within the area of sharpest vision (Fig. 393). On approaching the fovea, the ganglion-cells rapidly decrease in number until, at the centre of the depression, they and the nerve-fibre layer are entirely absent. The bipolar cells are

present as an irregular layer within the fused remains of the two plexiform layers. The most conspicuous elements are the visual cells, in this position represented solely by the cones, that have about twice their usual length and thickness, the increase in length being contributed by the outer segments. The cone-cell nuclei become removed from the external limiting membrane; the cone-fibres are therefore lengthened, pursue a radial direction, and constitute the so-called **fibre-layer of Henle.** Opposite the centre of the fovea,

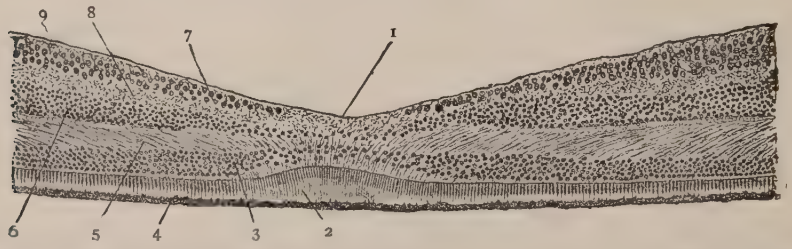


FIG. 393—Section of human retina through the macula lutea and its central area, the fovea centralis 1, fovea; 2, 3, cones and nuclei of cone-visual cells; 4, pigmented layer; 5, outer plexiform layer 6, bipolar cells; 7, ganglion-cells; 8, inner plexiform layer; 9, internal limiting membrane. × 80.

the choroid is thickened by an increase in the choriocapillaris. The yellow color of the macula is due to a diffuse coloration of the inner retinal layers.

The Ora Serrata.—The visual part of the retina ends anteriorly in an irregular line, the ora serrata. Here the retina diminishes in thickness in consequence of the abrupt disappearance of its nervous elements, and becomes reduced to two layers of cells. These continue over the pars plana and ciliary processes of the ciliary body and constitute the **pars ciliaris retinæ** (Fig. 394). The inner layer consists of unpigmented columnar cells

FIG. 394—Section of human retina through ora serrata, showing transition of pars optica into pars ciliaris. × 165.

while the outer layer is a direct continuation of the pigmented layer of the **pars optica retinæ** and is also densely pigmented. These two strata of cells are prolonged over the ciliary body and the iris as far as the pupil, over the iris constituting the **pars iridica retinæ.** As the inner columnar cells pass forwards, they gradually decrease in height and at the junction of the ciliary body and the iris the cells of both layers become deeply pigmented.

The **blood-vessels** of the retina are derived from the central artery, which enters the optic nerve behind the eyeball, and, with its accompanying vein, runs in the axis of the nerve until it emerges slightly to the nasal side of the centre of the optic disk. Here the artery divides into two short

superior and inferior branches, each of which subdivides into nasal and temporal branches which give off **end-arteries,** no anastomosis existing. The macular region is supplied by special twigs, the centre of the fovea, however, being free from blood-vessels. The larger branches course within the nerve-fibre layer, and send fine twigs to form an **inner** and an **outer plexus,** the former on the outer surface of the inner plexiform layer, and the latter within the inner nuclear layer. Beyond the outer plexiform layer the vessels do not penetrate, the visual cells being dependent for their nourishment upon the choriocapillaris of the choroid. Around the blood-vessels are spaces which may be injected from the subpial space of the optic nerve. By the same method communications may be demonstrated between (1) this space and the interstices between the nerve-bundles which converge towards the optic papilla, (2) a space between the membrana

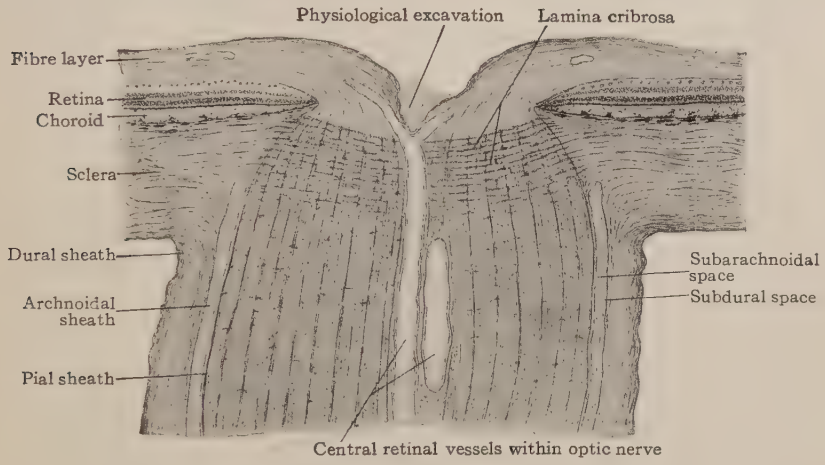


FIG. 395—Section of eyeball through entrance of optic nerve. × 20.

limitans interna and the hyaloid membrane of the vitreous, and (3) a narrow cleft between the pigmented cells and the layer of rods and cones.

The Optic Nerve.—The optic nerve is surrounded by the three sheaths—the dural, the arachnoidal, and the pial—which are continued over the nerve as prolongations of the corresponding brain-membranes. On reaching the eyeball the dural sheath bends directly outwards, its fibres commingling with those of the outer third of the sclera (Fig. 395); the arachnoid ends abruptly on the inner wall of the intervaginal space; whilst the pia arches outwards to form part of the inner third of the sclera, sending longitudinal fibres as far as the choroid. As the nerve-fibres leave the eyeball they traverse a fenestrated membrane, the **lamina cribrosa,** which is formed by interlacing bundles from the inner third of the sclera and from the pial sheath. As the nerve-fibres penetrate the lamina cribrosa they acquire their myelin sheaths and, in consequence, the optic nerve is enlarged one third in diameter. The nerve projects slightly into the eyeball on account of the thickness of the layer of arching nerve-fibres and forms, therefore, a

circular elevation, known as the **optic papilla,** about 1.5 mm. in diameter, the centre of which is modelled by a funnel-shaped depression, the so-called **physiological excavation,** or **blind-spot.** The axis of the nerve is occupied by the central artery of the retina, which gives off minute branches for the nutrition of the nerve, that anastomose with the pial vessels and, through the circulus arteriosus Zinni, with branches of the posterior ciliary arteries. In transverse sections the optic nerve appears as a mosaic of irregular polygonal areas composed of bundles of myelinated nerve-fibres surrounded by connective tissue envelopes. Although provided with myelin sheaths, the optic fibres are devoid of a neurilemma, in this respect agreeing with the nerve-fibres composing the central nervous system. The entire nerve corresponds to a huge funiculus, the perineurium being represented by the pial sheath and the endoneurium by the interfascicular septa of connective tissue prolonged from the pia between the bundles of fibres. Numerous connective tissue cells occur along the strands of fibrous tissue.

The Crystalline Lens

The lens, the most important part of the refractive apparatus of the eye is a biconvex body suspended from the ciliary body by the **suspensory ligament.** Its anterior surface supports the pupillary margin of the iris, its posterior surface resting in a depression, the **patellar fossa,** on the anterior surface of the vitreous body. It is completely transparent and enclosed in a transparent elastic membrane, the **lens capsule.** Together with the capsule, the lens measures from 8–9 mm. in its transverse diameter, and about 4 mm. in thickness from pole to pole.

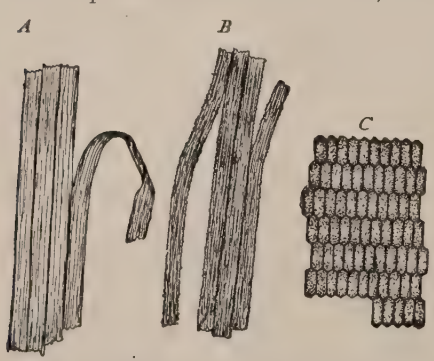


Fig. 396—Fibres of crystalline lens; *A*, *B*, fragments of isolated fibres; *C*, fibres in cross-section. × 275.

The **capsule,** which entirely surrounds the lens, is a transparent, structureless, highly elastic membrane, which, while resistant to chemical reagents, cuts easily, and then rolls outwards. It is thickest on the anterior surface, where it measures from 10–15 μ and thinnest at the posterior pole (5–7 μ). In the adult the lens is devoid of blood-vessels, but during a part of fetal life it is surrounded by a vascular network, the **tunica vasculosa lentis,** which is supplied chiefly by the hyaloid artery. This temporary vessel is the terminal branch of the central artery of the retina and passes from the optic disk forwards through the **hyaloid canal,** or canal of Cloquet, in the vitreous to the surface of the lens (Fig. 377). The vascular lens-tunic and the hyaloid artery are temporary structures and usually disappear before birth. Exceptionally they may persist, the tunic being represented anteriorly by the pupillary membrane and the artery by a fibrous strand within the vitreous, stretching from the optic disk towards the lens.

The anterior portion of the capsule is lined by a single layer of flat polygonal cells, the **epithelium of the lens capsule,** which represents morphologically the anterior wall of the original lens-vesicle. On approaching the equator of the lens, these cells become elongated and gradually pass into the lens-fibres which make up the greatest part of the lens.

The **lens-substance** is composed of long fibres, of compressed hexagonal outline in cross-sections, 5–11 μ broad and 2–4 μ thick, held together by an interfibrillar cement-substance. These fibres are modified epithelial elements, which develop by the elongation of the original ectodermic cells of the posterior layer of the primary lens-vesicle. The individual lens-fibres vary greatly in length, those forming the outer layers being longer and thicker than those which constitute the centre of the lens. The edges of the fibres are finely serrated, and, as the points of the serrations of adjacent fibres are in contact, fine intercellular channels are left for the passage of nutritive fluid.

FIG. 397—Portion of lens and its capsule; *A*, section through equator; *a*, capsule; *b*, epithelial cells, which at *z* transform into lens-fibres (*l*) with nuclei (*n*); *B*, fragment of capsule (*h*) with epithelium (*e*), surface view. × 130.

THE VITREOUS BODY

The vitreous body fills the space between the lens and the retina, being in close contact with the retina as far forwards as the ora serrata. Here it separates from the retina and passes to the posterior surface of the lens, presenting a shallow depression, the **hyaloid,** or **patellar, fossa,** on its anterior surface for the reception of the lens. The fresh vitreous is semi-fluid, perfectly transparent and consists of about 98.5 per cent. of water.

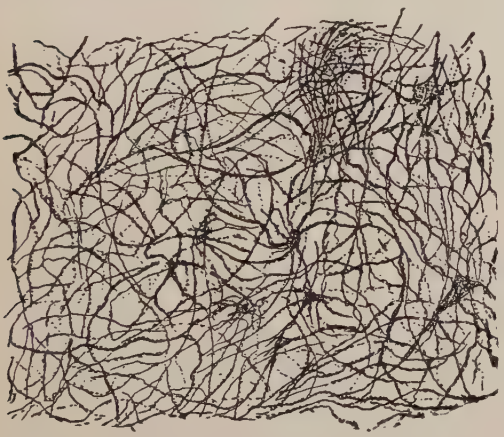


FIG. 398—Portion of vitreous body, showing feltwork of fibres and remains of cells. × 450. (*Retzius*)

The vitreous possesses a framework of delicate unbranched fibrils, which pass in all directions through the vitreous space and form the meshes in which the fluid constituents of the mass are held. The surface of the vitreous is enclosed by a delicate boundary layer, called the **hyaloid membrane** formed by condensations of the fibrils, arranged parallel to the surface and closely felted. It is, however, not a true membrane, but only a condensation of the vitreous fibres. The vitreous is attached firmly to the retina at the nerve-entrance and at the ora serrata, between these points the hyaloid being indistinct. As the vitreous leaves the retina, the boundary layer

becomes thicker, in some cases to become thin again or absent in the region of the patellar fossa. The adult vitreous ordinarily contains no cells, but some small round ones are occasionally seen near the surface, beneath or on the hyaloid membrane. They are amœboid, often contain vacuoles, and are modified leucocytes. In addition a few branched connective tissue cells may be present, as the remains of the mesodermic elements gaining entrance along with the blood-vessels during fetal life. The central part of the vitreous is occupied by a channel, the **hyaloid canal,** which is about 1 mm. wide and extends from the optic entrance towards the posterior pole of the lens. During fetal life this canal lodges the **arteria hyaloidea,** the continuation of the central artery of the retina.

The Suspensory Apparatus of the Lens

The lens is held in position by a series of delicate bands which pass from the vicinity of the ora serrata over the ciliary processes to be attached to the periphery of the lens. Near the ora serrata, the hyaloid membrane

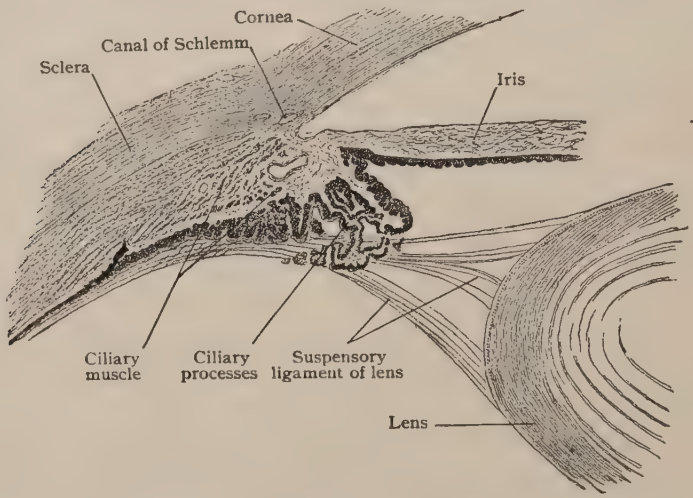


Fig. 399—Meridional section of ciliary region, showing ciliary processes and suspensory ligament of lens. × 20.

splits into two layers; the inner of these adheres to the vitreous as its investment, while the thicker outer layer passes over the ciliary region and bridges over the space between the processes and the lens. The fibres extending between the processes and the lens constitute the **suspensory ligament,** a structure of great importance not only for the support of the lens, but also in assisting the ciliary muscle in effecting the changes in the curvature of the lens incident to accommodation. The zonule includes a complex of fibres, some of which are firmly attached to the elevations of the ciliary processes, while others pass from the depressions between and along the sides of the processes. They all proceed across the circumlental space to find attachment into the capsule of the lens. Some of the fibres are inserted anterior to

the equator, others posterior to the equator, and some directly into the margin. Those inserted anteriorly arise behind and chiefly from the valleys between the ciliary processes, whilst those inserted into the equator come from the elevations of the processes. As they diverge to gain their insertion in the lens-capsule, the crossing fibres enclose an annular space, triangular in section, whose base is directed towards the lens equator (canal of Petit).

The Aqueous Humor and its Chamber

The aqueous humor is the transparent fluid which fills the space between the anterior surface of the vitreous body and the posterior surface of the cornea. In chemical composition it closely resembles the cerebro-spinal fluid, containing only traces of albumin and extractives, and differing from lymph in its low percentage of albumin. It is derived chiefly from the blood-vessels of the ciliary processes by the action of the double layer of cells covering the pars ciliaris retinæ. The aqueous humor, constantly produced is carried off through the spaces of Fontana into the canal of Schlemm, and also possibly through the tissue-spaces in the iris. With the exception of a few migratory leucocytes, the aqueous humor is devoid of morphological elements.

The space occupied by the aqueous humor is incompletely subdivided by the iris into two compartments, the anterior and posterior chambers of the eye. The **anterior chamber,** is bounded in front by the cornea and behind by the iris and lens and has a depth at its centre of from 7.5–8.5 mm. The **posterior chamber** is the small annular space, triangular in cross-section, which has for its anterior boundary the iris, is limited laterally by the ciliary processes, and medially and posteriorly by the lens and the vitreous body. The spaces between the fibres of the suspensory ligament communicate with the posterior chamber, are filled with aqueous humor, and are, therefore, only a part of the posterior chamber.

THE EYELIDS AND CONJUNCTIVA

The eyelids, or **palpebræ,** are two movable folds of integument—an upper and a lower—strengthened along their free margins by a lamina of dense fibrous tissue, the **tarsal plate,** and modified on their deeper aspect so that this surface resembles a mucous membrane, the **conjunctiva.** The free border of the lid presents a well-defined posterior margin, along which open the minute ducts of the **tarsal glands,** whilst the anterior margin is rounded and passes insensibly into the adjoining external skin-surface and is beset with the eyelashes. The latter, the **cilia,** are stiff outwardly curving hairs, which number from 150–175 in the upper lid and about half as many in the lower. That part of the narrow conjunctival sac which covers the posterior surface of the lids constitutes the **palpebral conjunctiva** and that reflected onto the eyeball is the **bulbar conjunctiva,** while the bottom of the groove, where these two portions are continuous, is known as the **fornix conjunctivæ.** The **lacrimal lake** is the shallow bay into which the conjunctival sac is

prolonged for about 5 mm. between the medial ends of the eyelids. It contains an irregularly oval or comet-shaped elevation, the **lacrimal caruncle.** The latter consists of an islet of modified skin from which project usually about a dozen minute and scarcely visible hairs, provided with large sebaceous and smaller sweat-glands and embedded in a cushion of fatty tissue. Just to the outer side of the caruncle lies a vertical crescentic fold, the **plica semilunaris,** which frequently contains a minute plate of hyaline cartilage as the vestige of the stronger bar in the nictitating membrane, which the fold represents. Likewise the small group of alveoli sometimes found within the base of the fold is regarded as the homologue of the Harderian gland. Where the boundaries of the lacrimal lake pass into the edges of the upper and lower eyelids are two little elevations, the **lacrimal papillæ,** each of which is pierced by a minute aperture, the **punctum lacrimalis,** that marks the beginning of the canals by which the tears are normally carried off from the conjunctival sac.

The Eyelids.—The eyelid comprises five layers which, from without inwards, are: (1) the **skin,** (2) the **subcutaneous tissue,** (3) the **muscular layer,** (4) the **tarso-fascial layer,** and (5) the **conjunctiva.**

The **skin** covering the outer surface of the eyelids is characterized by its unusual delicacy, being thin and beset with very fine downy and widely scattered hairs, provided with sebaceous follicles; small sweat-glands also occur.

The **subcutaneous tissue** is distinguished by the absence of fat, its loose texture, and great extensibility and elasticity. In consequence of these properties, it sometimes becomes the seat of extensive swelling after edema or hemorrhage.

The **muscular layer,** for the most part the annular bundles of the orbicularis palpebrarum, is also blended with the subcutaneous tissue as to be practically embedded within the latter. In vertical sections of the eyelid, (Fig. 400) the circularly arranged muscular bundles show as transversely cut groups of muscle-fibres enclosed by condensations of the surrounding areolar tissue. A distinct annular tract, the **ciliary bundle,** or **muscle of Riolan,** lies close to the free border of the lid, chiefly between the tarsal plate and the hair-follicles, in part often also between the conjunctiva and the tarsus. In the upper lid, in addition to the circular bundles of the orbicularis palpebrarum, the terminal strands of the longitudinal fibres from the levator palpebræ superioris descend along the deeper surface of the first-named muscle. Some of these penetrate between the circular bundles and end in the deeper layer of the skin; others descend more vertically to find their insertion in the upper border of the tarsal plate. Under the name **tarsal muscles,** or **muscles of Müller,** are described the uncertain bundles of involuntary muscle found in the vicinity of the convex borders of the tarsi. Those within the upper lid arise from the tendon and intermingle with the fibres of the levator palpebrarum and insert either into the upper border of the tarsal plate or into the adjacent fibrous tissue. In the lower lid, they are less numerous and regular and extend from the fornix conjunctivæ to the lower border of the tarsus.

The **tarso-fascial layer** is represented next the margins of the lids by the tarsal plates and beyond the latter by the looser fascial connective tissue, in which, especially towards the attached ends of the lids, may be groups of fat cells.

The **tarsal plates** are two crescentic lamellæ of dense fibrous tissue, one in each lid, that occupy the margins of the eyelids, to the maintenance

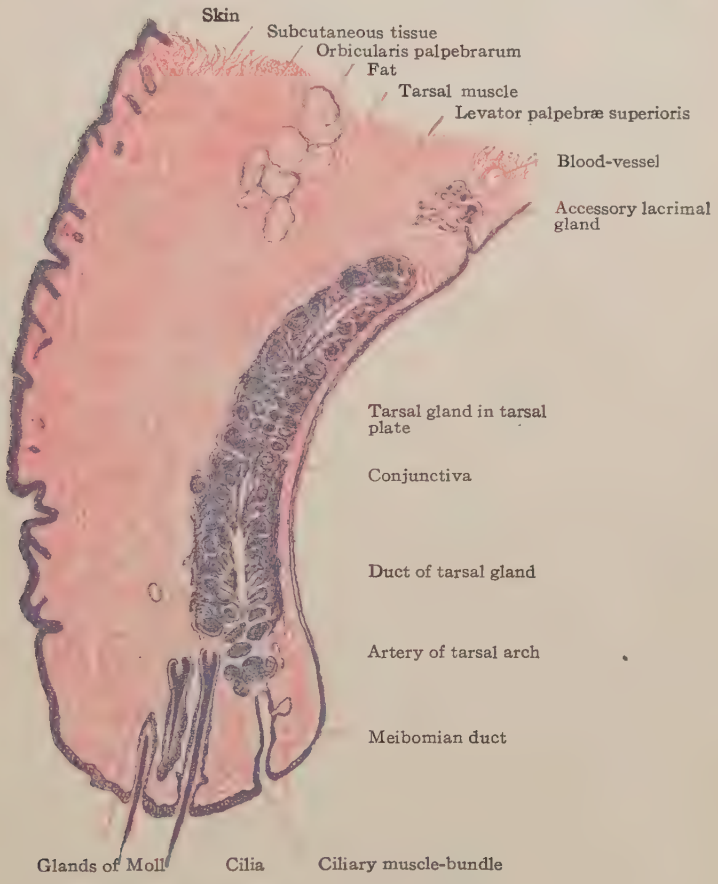


FIG. 400—Sagittal section of upper eyelid of child. × 15.

of whose form they largely contribute. The upper tarsus is the larger. The plates are approximately 1 mm. in thickness and consist of densely felted fibrous tissue. The tarsal plates lodge the linear series of the **Meibomian, or tarsal, glands.** These structures, between twenty and thirty in number in the upper lid and about one third less in the lower one, consist of a chief tubular duct, placed vertically and lined by stratified squamous epithelium, which is beset with numerous simple or branched, irregular, flask-shaped alveoli. The latter contain cuboidal epithelial elements that resemble in appearance and condition those found in sebaceous follicles, to which class,

in fact, the tarsal glands belong. They secrete an oily substance, **sebum palpebrarum,** which is discharged through the minute punctiform orifices of the ducts seen as a row of dark points just external to the sharp conjunctival border of the eyelid. In this manner the latter is kept lubricated, and thus, under usual conditions, maintains an effective barrier against the overflow of the tears from the conjunctival sac. Within the free edge of the eyelids, just in advance of the tarsal plates, lie the **glands of Moll** and the **glands of Zeiss.** The former are coiled tubules, resembling modified sweat-glands; the latter sebaceous glands, the ducts of which usually open close to or into the mouths of the follicles of the eye-lashes.

The **palpebral conjunctiva** lines the ocular surface of the eyelids, and has the general appearance of a mucous membrane. Since the eyelids are developed as integumentary folds, the conjunctiva has the same origin as the skin of the lids. These integumentary folds grow out early in the third month of fetal life, meet, and fuse along their epithelial margins. They remain fused until the end of the sixth month or the beginning of the seventh month of fetal life. In some animals this period of fusion extends into the second week of post-natal life (cat, dog, rabbit). Over the tarsi the palpebral conjunctiva is so tightly adherent to the underlying fibrous plate, that the tunica propria is reduced to an insignificant layer and the Meibomian glands shimmer through the smooth translucent conjunctiva and appear as parallel stripes. On gaining the convex border of the tarsal plates, the conjunctiva becomes loose and movable since the tunica propria which here connects the epithelium with the underlying facial tissue, is plentiful. The small tubules, **glands of Henle,** occupy the subepithelial tissue of this part of the conjunctiva. In the fornix and its vicinity minute **lymph-nodules** occur, either discrete or in small groups. In the same locality and at the convex borders of the tarsi, small nests of tubular alveoli, known as **accessory tear-glands** are found. They are much more numerous in the upper than in the lower lid.

The **bulbar conjunctiva** passes from the fornix onto the anterior part of the eyeball, over which it extends as far as the corneal margin, at which point (**limbus corneæ**) the tunica propria ends and the epithelium alone continues uninterruptedly over the cornea. During its passage from the free edge of the eyelid to the cornea, the character of the **conjunctival epithelium** varies in different parts of the sac. Thus, at the border of the lids and for a few millimeters over the tarsi, it resembles the epidermis in being stratified squamous. Towards the convex border of the tarsal plates the squamous type gives place to the cylindrical; in the retrotarsal fossa, throughout the fornix and for a short distance over the eyeball, the epithelium is exclusively columnar, varying in thickness and in the number of its layers; while over the cornea and adjacent parts of the sclera, the epithelium is again stratified squamous.

The **blood-vessels** form an arch in each lid along the base of each tarsus, between the latter and the orbicularis muscle, from which perforating twigs penetrate the tarsal plates for the supply of the Meibomian glands and adjacent conjunctiva. The **lymphatics** are arranged in two sets, a pretarsal

and a post-tarsal, the networks of which are connected by vessels which pierce the tarsi. The former receives lymph from the skin and muscles, the latter from the Meibomian glands and the conjunctiva. The **nerves** supplying the eyelid include sensory, motor, and sympathetic fibres. The main branches lie between the tarsi and the orbicularis, sending branches forwards to the skin and backwards through the tarsi to the Meibomian glands and the conjunctiva. Those to the conjunctiva lose their myelin coat and terminate either in free arborizations, beneath or among the epithelial cells, or in the end-bulbs. The latter are particularly numerous along the lid-margin, but occur also in the palpebral and bulbar conjunctiva and at the corneal border. The sympathetic fibres supply the tarsal and other lid-glands and send filaments to the walls of the blood-vessels.

THE LACRIMAL APPARATUS

The lacrimal apparatus consists of the gland secreting the tears, situated in the anterior and outer portion of the orbital cavity, and the system of canals by which the tears are conveyed from the mesial portion of the conjunctival sac to the inferior nasal meatus.

The **lacrimal gland** resembles in shape and size a small almond and

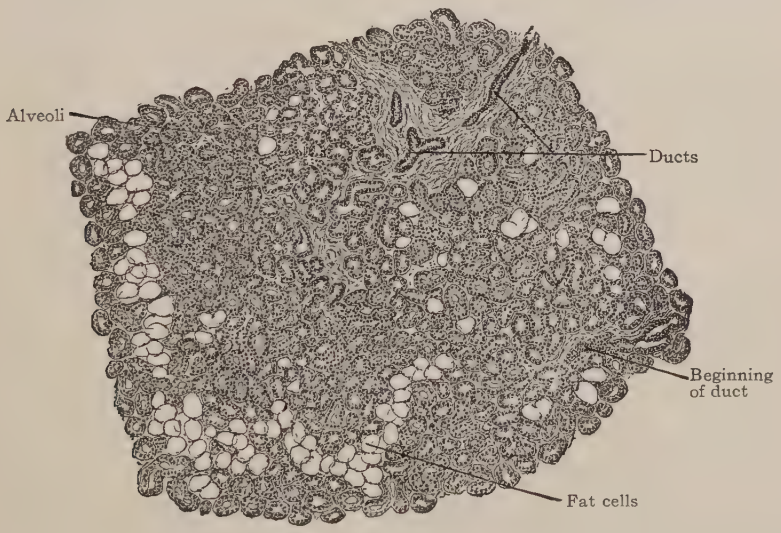


FIG. 401—Section of lacrimal gland, showing general arrangement of alveoli. × 20.

consists of two fairly distinct parts, the superior **orbital portion** and the inferior **palpebral,** or **accessory portion.** The former occupies the fossa lacrimalis in the frontal bone and is the larger portion, measuring 20 mm. in length and 12 mm. in breadth. The lower portion of the gland, **glandula lacrimalis inferior,** is smaller than the upper and separated from the latter by a fascial expansion.

The **ducts** from both portions of the gland are exceedingly fine, those from the upper portion, from three to six in number, passing downward through the inferior portion. Some of the ducts from the lower gland join those coming from above, while others run independently. They are lined with a double layer of columnar epithelial cells. In all about a dozen ducts open into the conjunctival sac along a line just in front of the fornix. In structure the glands correspond to the tubo-alveolar type and resemble the serous glands in their general character. The alveoli of the lower portion are separated by robust septa of connective tissue, which contain considerable lymphoid tissue.

Accessory lacrimal glands are found in both the upper and lower fornices, from eight to twenty being present in the upper lid, and from two to four in the lower. They are very small and situated chiefly near the outer angle of the palpebral fissure.

The **lacrimal passages** begin by minute openings, the **lacrimal puncta,** which are usually placed at the summit of the conical **lacrimal papillæ.** The puncta lead into the **lacrimal canaliculi,** which at first are vertically directed, then bend abruptly, take a nearly horizontal course, and empty into the lacrimal sac. Each canaliculus is from 6–7 mm. in length. Its lumen measures only .1 mm. in diameter at the punctum, presents a diverticulum of 1 mm. at the bend, and continues with an approximately uniform calibre of .5 mm. in its horizontal portion. The canaliculus possesses a lining of stratified squamous epithelium, which rests upon a delicate tunica propria rich in elastic fibres, muscular fibres from the orbicularis palpebrarum affording additional support. The muscle-bundles run parallel to the horizontal portion of the canaliculus but are arranged as a circular sphincter about the vertical portion.

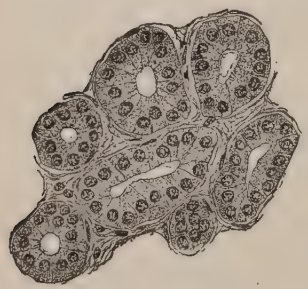


Fig. 402—Alveoli of lacrimal gland more highly magnified. × 235.

The **lacrimal sac** may be regarded as the upper dilated portion of the naso-lacrimal duct, the lower part of which passes through a bony canal and opens into the **inferior nasal meatus.** The sac is about 15 mm. long, and 6 mm. in diameter when distended. The wall of the sac is composed of a fibro-elastic tunica propria of lymphoid character and is loosely connected with the periosteum by a stratum rich in veins. A few small branched tubular glands are usually present. It is lined with a double layer of columnar epithelial cells, which in part are provided with cilia.

The **naso-lacrimal duct,** the lower portion of the tear-passage, varies from 12–24 mm. in length, and is from 3–4 mm. in diameter. It is lined with columnar epithelium and may contain small glands in the lower portion. It is separated from the periosteum by areolar tissue and a venous plexus.

THE EAR

THE ORGANS OF HEARING AND OF EQUILIBRIUM

The auditory organ is conventionally decribed as the external, middle, and internal ear—structures lodged entirely or in part within the temporal bone. The **external ear** includes the auricle and the external auditory canal, or meatus; the **middle ear** the tympanum, the Eustachian tube, and the mastoid air-cells; and the **internal ear** the labyrinth, with the peripheral ramifications of the auditory nerve. Such division, moreover, is justified by the developmental history of the organ, since the internal ear is developed essentially from the otic vesicle which gives rise to the complicated membranous labyrinth; the middle ear largely from the first pharyngeal pouch; whilst the external ear represents the deepened and modified boundaries of the first external branchial cleft.

THE EXTERNAL EAR

The external ear includes (1) the **auricle,** or **pinna,** the appendage projecting from the side of the head for the collection of the sound-waves, and

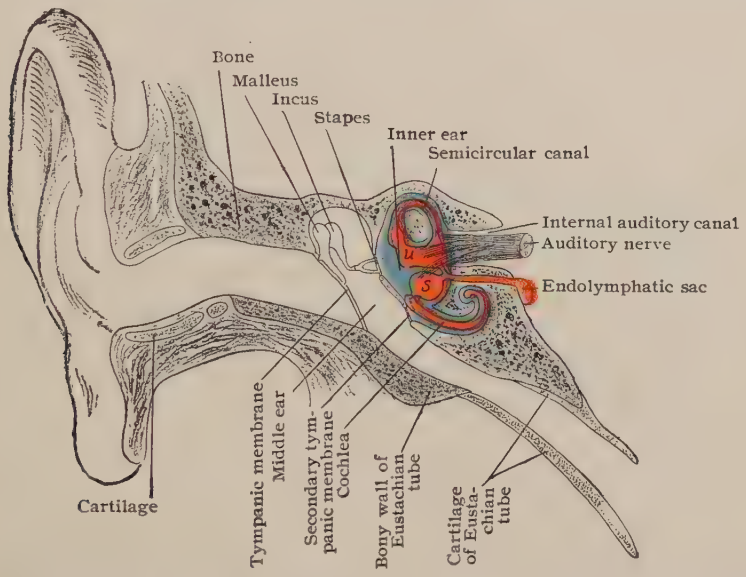


FIG. 403—Diagram showing three subdivisions of ear; *u*, utricle; *s*, saccule; blue is the perilymph within the bony labyrinth, red the endolymph within the membranous labyrinth of the internal ear. (*Modified from Schwalbe.*)

(2) the **external auditory canal,** which conveys these stimuli to the tympanic membrane, the flexible partition closing the canal and separating it from the middle ear.

The Auricle.—The outwardly directed surface of the auricle is irregularly concave and presents several well-marked depressions and elevations,

which depend, for the most part, upon the corresponding modelling of the underlying cartilage.

The auricle consists of integument and an enclosed plate of yellow elastic cartilage, continuous with that of the meatus. It is also provided with several ligaments and rudimentary muscle. The lobule, however, contains no cartilage, but only fibrous tissue and fat enclosed within the integumentary fold. The skin of the auricle is thin and closely adherent to the cartilage, especially on the outer surface. In certain parts it contains fine hairs and

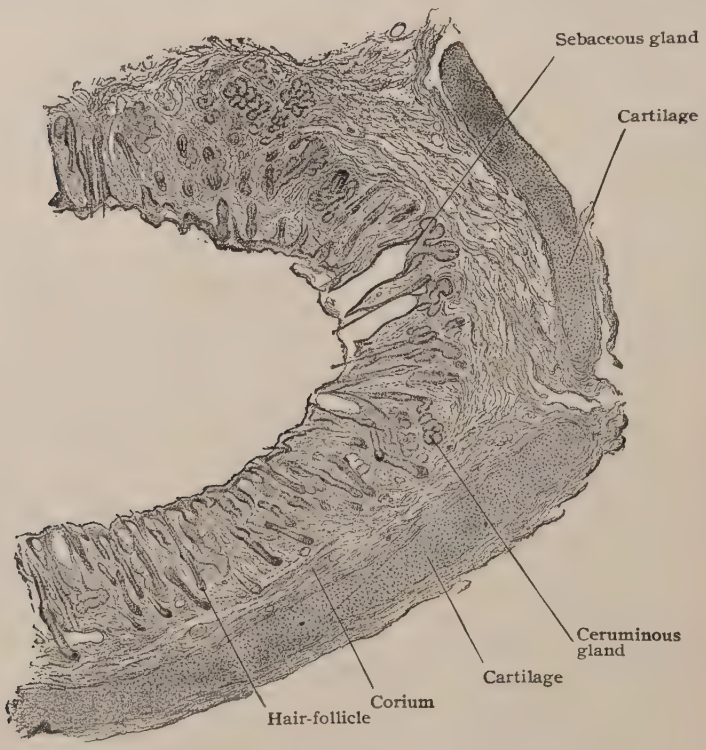


FIG. 404—Section of skin lining cartilaginous part of external auditory canal. × 30.

sebaceous and sweat-glands. The hair-follicles are especially abundant over the tragus, antitragus, and the notch lying between them, the hairs guarding the entrance into the external auditory canal, known as **tragi,** being exceptionally long. The sebaceous glands are especially well developed in the wall of the concha, the deepest part of the concavity adjoining the entrance to the meatus.

The External Auditory Canal.—The external auditory canal, or **meatus acusticus,** leads from the cavity of the concha to the tympanic membrane, which closes its inner extremity. It is composed of an outer cartilagino-membranous (cartilaginous) and an inner bony portion, both of which, as well as the external surface of the tympanic membrane, are lined

by skin. The cartilagino-membranous part contributes something more than one third of the entire length of the canal, and is a continuation of the cartilage of the auricle. The cartilage of the canal, histologically of the elastic type, does not form a complete tube, but is deficient at its upper back part, where the intervening space is filled in by fibrous tissue. On approaching the bony portion, this deficiency in the cartilage is more marked and the fibrous tissue correspondingly increased.

The **skin** lining the outer portion of the canal is closely attached to the underlying cartilage and measures about 1.5 mm. in thickness. It is much thinner within the bony canal, except along the roof, where it remains relatively thick. Over the outer surface of the tympanic membrane, the skin is reduced to a very delicate and smooth investment. Numerous fine hairs and large **sebaceous glands** occur in the cartilaginous portion, but diminish in size and frequency towards the bony canal, in which they are entirely wanting. Within the cartilaginous meatus and along the roof of the bony tube, the skin is closely beset with the large coiled **ceruminous glands** which resemble in structure modified sweat-glands. Like the latter, the ceruminous glands consist of a deeper and wider coiled portion, the **secretory segment,** and a long narrow **excretory duct** which ends in most cases independently on the free surface of the skin. Sometimes, particularly in the very young child, it may open into the duct of a sebaceous gland. The cuboidal secreting cells contain yellowish-brown pigment particles and granules resembling fat. The **ear-wax,** or **cerumen,** is, as usually found, the more or less dried mixture of the secretions derived from both varieties of glands, together with discarded squamous epidermal cells.

The **blood-vessels** distributed to the interior of the external auditory canal pierce the membranous roof of the cartilaginous meatus and the associated fibrous tissue and form capillary networks within the perichondrium and periosteum and, within the skin, around the glands and the hair follicles. The **lymphatics** of the external auditory canal arise from a cutaneous network, from which trunks pass in three general groups, as do those of the auricle. The **nerves** supplied to the external auditory canal, derived from the auriculo-temporal branch of the trigeminus and from the auricular branch of the vagus are chiefly myelinated and sensory. Sympathetic fibres end in connection with the glands.

THE MIDDLE EAR

The middle ear includes three subdivisions; the **tympanic cavity,** the **Eustachian tube,** and the **mastoid cells.**

It is an irregular air-chamber, beginning on the lateral wall of the nasopharynx with the Eustachian tube, which leads upwards, backwards, and outwards, for about one inch and a half into the temporal bone. Opposite the external auditory canal, it widens into the tympanic cavity and continues backwards into the mastoid cells.

The Tympanic Cavity.—The tympanic cavity is an irregular space within the temporal bone, lying between the internal ear and the external

auditory canal. It is lined with mucous membrane and contains, in addition to the air which enters by way of the Eustachian tube, the chain of ear-ossicles.

The Membrana Tympani.—The tympanic membrane, or drum-head, is a delicate transparent disk, irregularly oval or ellipsoidal in outline and concave on its outer surface. It is about .10 mm. thick, except at the periphery, where it is thickened.

Embedded in the tympanic membrane is the handle of the malleus (Fig. 405), which extends from a point near its middle, upwards and forwards toward its periphery. At its lower end, the handle of the malleus is flattened laterally and broadened at the **umbo,** which corresponds to the deepest part of the concavity of the membrane.

FIG. 405—Frontal section through tympanic membrane and malleus, showing long process of the latter embedded within membrane. × 8. (*Preparation by Dr. Ralph Butler.*)

The tympanic membrane includes three main layers: (1) the **middle, or fibrous, stratum;** (2) the **external** or **cutaneous layer,** the prolongation of the skin lining the external auditory canal; and (3) the **internal,** or **mucous, membrane,** a continuation of the mucous membrane clothing other parts of the tympanic cavity.

The **fibrous layer,** the membrane proper, represents the mesodermic portion of the drum-head and consists of an outer stratum of radially disposed fibres which diverge from the malleus towards the periphery of the membrane, and an inner stratum of circular fibres, concentrically arranged and best developed near the periphery of the membrane, but absent at the umbo. The radiating fibres, on the contrary, become more dense at the umbo. Connective tissue cells, spindle-shaped in longitudinal and stellate in cross-section, lie between the fibres of the two layers. At the periphery of the membrane proper, the fibres, especially those of the radial stratum, are connected with those of a ring of thick connective tissue, the **annulus fibrosus.** The fibres of the annulus run in various directions, but for the most part radially, that is, towards the tympanic membrane proper (Fig. 406).

The **cutaneous layer** consists of a thin epidermal stratum, composed of

two or three rows of cells and a delicate sheet of connective tissue; neither a definite corium nor papillæ are present.

The **mucous membrane** covering the inner surface of the drum-head consists of a scanty layer of connective tissue, invested with a single layer of large low non-ciliated epithelial cells.

The **blood-vessels** of the tympanic membrane include arteries arranged as an outer and an inner set, separated by the fibrous layer of the membrane. Each of these sets forms a plexus with a large branch extending downwards along the malleus-handle and another around the periphery

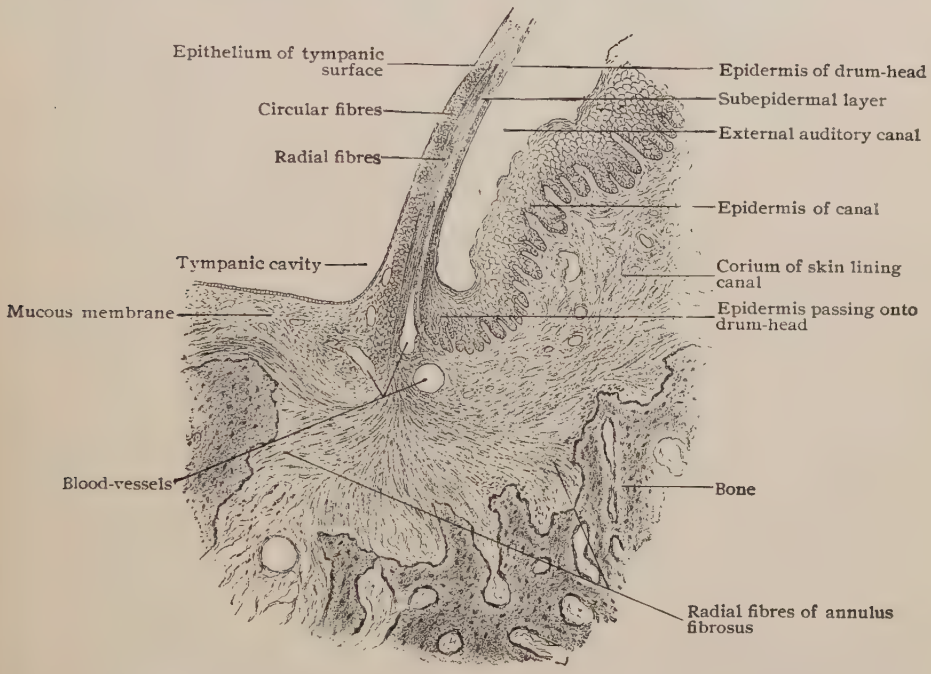


FIG. 406—Section through attached margin of tympanic membrane, showing continuation of skin and mucous membrane over its outer and inner surfaces respectively. × 75. (*Preparation by Dr. Ralph Butler.*)

of the membrane, these two branches being connected by numerous radiating twigs. Perforating vessels connect the two sets of arteries, especially along the malleus-handle and at the periphery of the membrane. The **veins** are most numerous at the handle of the malleus and periphery of the membrane and communicate with those of the external meatus and tympanic cavity. The **lymphatics** are arranged similarly to the blood-vessels in two sets, one under the skin and the other under the mucous membrane, which communicate freely with each other. The **nerves** supplying the tympanic membrane accompany, for the most part, the blood-vessels and, in addition to supplying the latter, form both a subcutaneous and a submucous plexus.

The **auditory ossicles** are three small bones that form a chain extending

across the upper part of the tympanum from the tympanic membrane to the labyrinth. The outermost of these, the **malleus** (hammer), is attached to the tympanic membrane; the innermost, the **stapes** (stirrup), is fixed in the oval window, and between these two bones and connected with both of them, lies the third link in the chain, the **incus** (anvil). Their surfaces of contact are covered with articular cartilage and enclosed to form miniature true joints, provided with fibrous capsular ligaments and synovial membranes. The bones do not lie exposed within the tympanic space, but are invested with a continuation of the general mucous membrane which has enfolded them.

The Eustachian Tube.—The Eustachian tube, or **tuba auditiva,** is a

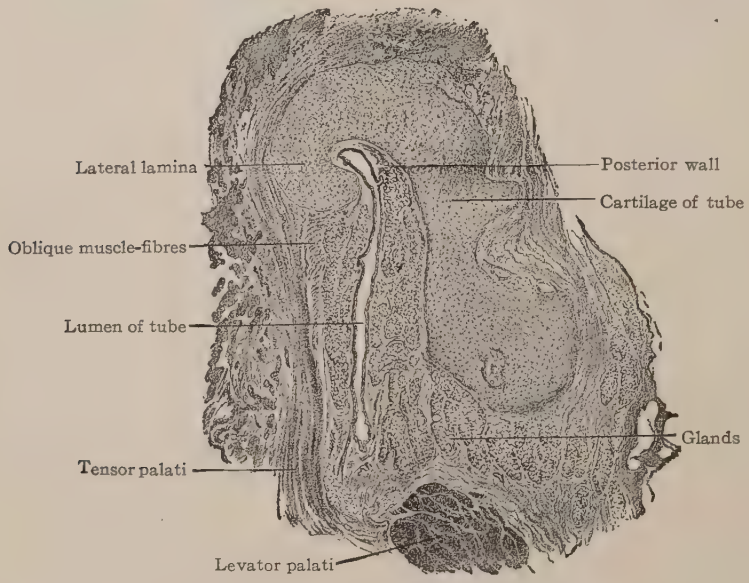


FIG. 407—Section across cartilaginous part of Eustachian tube. × 7.

canal, partly bony and partly cartilaginous, extending from the lateral wall of the naso-pharynx backwards, upwards, and outwards to the anterior part of the tympanum. In the adult it measures about 37 mm. in length, of which approximately the upper third (tympanic portion) belongs to the bony division, and the remainder to the cartilaginous division.

The posterior wall of the pharyngeal portion is formed by a plate of cartilage, the upper margin of which is curled outwards upon itself and appears as a hook on transverse section. At birth the cartilage is entirely of the hyaline variety, but later this is more or less extensively replaced by fibro-cartilage, except in the upper part, where the hyaline cartilage persists.

The **mucous membrane** of the Eustachian tube lines the tube throughout its length, but differs somewhat in the cartilaginous and osseous portions. That in the former resembles the mucous membrane of the naso-pharynx, with which it is directly continuous, while that of the osseous division

resembles, to some extent, the mucous membrane of the tympanic cavity. The **epithelium** of both divisions is of the ciliated stratified columnar type, with some goblet-cells. The cells in the pharyngeal division, especially in the lower part, are taller than those of the tympanic portion, which are low cuboidal. In the tympanic portion the mucous membrane is closely united with the periosteum and contains very few mucous glands and little or no lymphoid tissue. In the cartilaginous division, on the contrary, the epithelium overlies a layer of such tissue, often called the **tubal tonsil.** This tissue is especially abundant in children, and beneath it are found numerous mucous glands, which open on the free surface of the tube. These glands extend nearly to the perichondrium and sometimes can be traced even through the fissures in the cartilage into the surrounding connective tissue. A considerable amount of adipose tissue often occupies the submucosa of the lower and lateral walls. The submucous layer is well developed in the cartilaginous division of the tube, particularly in the outer membranous wall. It consists of loosely arranged fibro-elastic tissue, which supports the mucous glands and the larger vessels and nerves.

The **muscles** of the Eustachian tube are the **levator palati,** which lies beneath and to the inner side of the tube, and the **tensor palati,** which lies to its outer side. By reason of the intimate attachment which both muscles have to the cartilage of the tube, since both take partial origin from this structure, contraction of their fibres, particularly those of the tensor palati, tends to draw apart the walls of the canal; they thus serve as dilators.

The Mastoid Cells.—The tympanic cavity communicates posteriorly, through the antrum, with a variable number of irregular pneumatic cavities, the mastoid cells, so called because the majority of these spaces occupy the mastoid process. Unlike the antrum, these air-cells are not developed at birth. As the mastoid process develops, the original diploetic structure is usually more or less replaced by larger cavities filled with air and lined by a very thin mucous membrane, which is continuous with that of the antrum and of the tympanic cavity. This mucous membrane is closely united with the periosteum and possesses a layer of low non-ciliated squamous epithelium.

THE INTERNAL EAR

The internal ear consists essentially of a highly complex membranous sac, connected with the peripheral ramifications of the eighth nerve, and a bony capsule which encloses all parts of the membranous structure and is embedded within the substance of the petrous portion of the temporal bone. These two parts, known respectively as the **membranous** and the **bony labyrinth,** are not everywhere in close apposition, but in most places are separated by an intervening space filled with a fluid, the **perilymph,** the inner sac lying within the osseous capsule like a shrunken cast within a mould. The membranous labyrinth is hollow, and everywhere filled with a fluid, called the **endolymph,** which nowhere gains access to the cavity occupied by the perilymph. The internal ear is closely related with the lamina cribrosa of the internal auditory meatus on the one side, and with the inner

wall of the tympanic cavity on the other. Its entire length is about 20 mm., and its long axis corresponds closely with that of the pyramidal, or petrous, portion of the temporal bone. The irregular cavity of the bony labyrinth comprises three subdivisions: a middle one, the **vestibule;** an anterior one, the **cochlea;** and a posterior one, the **semicircular canals.** Both the front and hind divisions communicate freely with the vestibule. Although corresponding in its general form with the bony compartments of the cochlea and semicircular canals, the membranous labyrinth less accurately agrees in its contour with the bony vestibule, since, instead of presenting a single cavity, it is subdivided into two unequal compartments, known as the saccule and the utricle, which are lodged within the bony vestibule. The divisions of the membranous labyrinth are, therefore, four, which from before backwards are: the **membranous cochlea,** the **saccule,** the **utricle,** and the **membranous semicircular canals.**

The Osseous Labyrinth

The **vestibule,** the middle division of the bony labyrinth, lies between the cochlea in front and the semicircular canals behind, and communicates freely with both. The lateral (outer) wall separates it from the tympanic cavity and contains the **oval window** with the foot-plate of the stapes. The margin of the window and the foot-plate are covered with hyaline cartilage and connected by fibro-elastic tissue, thus preventing the escape of the perilymph from the vestibule. The anterior wall of the vestibule is pierced by the large opening leading into the scala vestibuli of the cochlea. Posteriorly the vestibule directly communicates with the semicircular canals by five round openings.

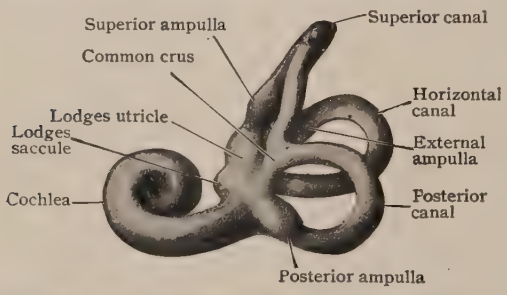


Fig. 408—Cast of right bony labyrinth, mesial aspect. × 2.

The three **bony semicircular canals**—the **superior,** the **posterior,** and the **horizontal**—lie behind the vestibule, their disposition being such that the planes of the three canals correspond with the sides of the corner of a cube. Each canal possesses at one end a dilatation, called the **osseous ampulla.** The semicircular canals open into the posterior part of the vestibule by five apertures, the undilated ends of the superior and posterior canals joining to form a common limb (Fig. 408). The horizontal canal alone communicates with the vestibule by two independent openings.

The vestibule and the bony semicircular canals are lined by a very thin periosteum of fibrous tissue, containing flattened connective tissue cells. Endothelium everywhere lines the perilymphatic space between the membranous and osseous canals, covering the free inner surface of the periosteum the fibrous trabeculæ, and the outer, or perilymphatic, surface of this part of the membranous labyrinth.

The **bony cochlea** constitutes the anterior part of the labyrinth and appears as a short blunt cone, about 5 mm. in height, whose base lies in the anterior wall of the outer end of the internal auditory meatus. Its apex is directed horizontally forwards and outwards. The bony cochlea consists essentially of a tapering central column, the **modiolus,** around which the bony canal, about 30 mm. long, makes something more than two and a half spiral turns, the **basal, middle,** and **apical.** The conical modiolus has a broad concave **base,** which forms part of the base of the cochlea, and a small **apex,** which extends nearly to the apex of the cochlea, or the **cupola.** It is much thicker within the lowest turn of the canal than above, and is pierced by many small canals for the nerves and vessels to the spiral lamina. The axis of the modiolus, from base to apex, is traversed by the **central canal,** while a more peripherally situated channel, the **canalis spiralis,** encircles the

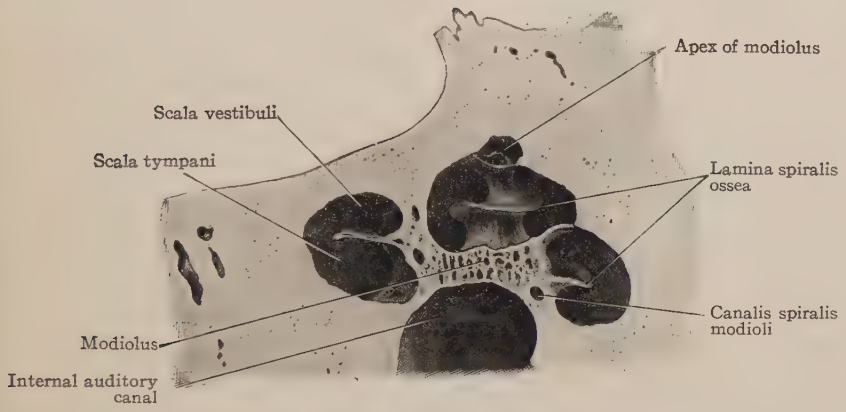


FIG. 409—Cochlea and bottom of internal auditory canal exposed by vertical section; cochlea rests with its base downwards and apex pointing upwards. × 5.

modiolus and contains the spiral ganglion and a spiral vein. Projecting at a right angle from the modiolus into the canal of the bony cochlea is a thin shelf of bone, the **lamina spiralis ossea,** which is made up of two delicate bony plates between which are fine canals containing the branches of the cochlear nerve. The partial division of the canal of the bony cochlea effected by the osseous spiral lamina is completed by the membranous spiral lamina which stretches from the free edge of the osseous lamina to the outer wall of the canal (Fig. 413). The upper division of the canal is called the **scala vestibuli** and communicates with the vestibule, whilst the lower division, the **scala tympani,** would open into the tympanic cavity, were it not separated from that space by the **secondary tympanic membrane.** The latter is a thin fibro-elastic sheet, covered internally with endothelium and externally with epithelium. The scala vestibuli and scala tympani are continuous with each other through an opening, the **helicotrema,** at the apex of the cochlea.

The Membranous Labyrinth

The membranous labyrinth lies within the bony labyrinth, which it resembles in general form. This agreement is least marked within the vestibule, since here the single division of the bony capsule is occupied by two compartments of the membranous sac, the utricle and the saccule. The membranous labyrinth comprises: (1) the **utricle** and the **saccule,** which, with the beginning of the **ductus endolymphaticus,** lie within the vestibule (2) the three **membranous semicircular canals** lodged within the bony semicircular canals; and (3) the **membranous cochlea**, or **ductus cochlearis,** enclosed within the bony cochlea. Within the ductus cochlearis is the receptor for hearing and within the semicircular canals, utricle, and saccule are the receptors for equilibrium. The membranous labyrinth is attached,

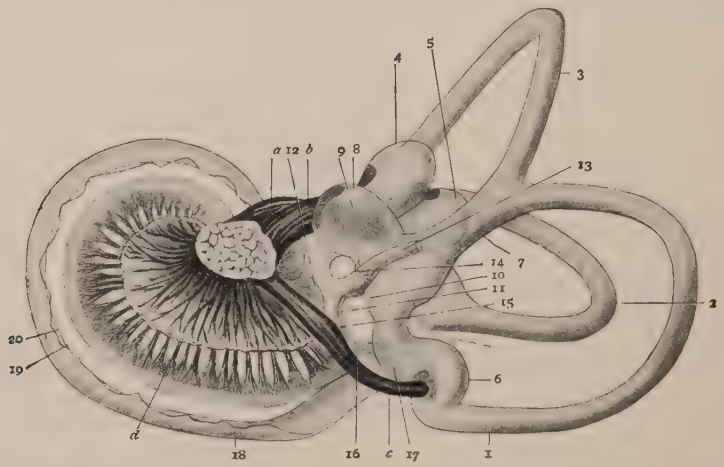


Fig. 410—Membranous labyrinth of five-months fetus, postero-mesial aspect. 1, 2, 3, posterior, horizontal, and superior semicircular canals; 4, 5, 6, their ampullæ; 7, common crus of superior and posterior canals; 8, 9, recess and macula of utricle (10); 11, saccule and its macula (12); 13, ductus endolymphaticus; 14, utriculo-saccular canal; 15, canalis reuniens, opening at 16 into cochlear duct; 17, blind sac of cochlear duct (18); 19, basilar membrane, 20, ligamentum spirale; *a*, facial nerve; *b*, vestibular nerve; *c*, branch of vestibular nerve to posterior canal; *d*, branches of cochlear nerve to Corti's organ. ×6. (*Retzius.*)

especially in certain places, by connective tissue to the inner wall of the bony capsule. The interval between the membranous and bony labyrinths, largest in the scalæ tympani and vestibuli of the cochlea and in the vestibule constitutes the **perilymphatic space** and contains the **perilymph.** The fluid within the membranous labyrinth, the **endolymph,** can pass from one part of the labyrinth to another, although the connections between saccule and utricle, and between saccule and cochlear duct become much constricted (Fig. 403).

Structure of the Utricle, Saccule, and Semicircular Canals.—The walls of these subdivisions of the membranous labyrinth are made up of (**a**) an outer fibrous **connective tissue lamella** and (**b**) an inner **epithelial lining,** the latter consisting throughout the greater part of its extent of a single layer of thin flattened cells. At six places, however, there are areas of neuro-epithelium, innervated by the vestibular division of the eighth nerve.

Three are called **maculæ staticæ,** one in the saccule and two in the utricle; three are called **cristæ staticæ,** one in each of the three ampullæ.

The **maculæ staticæ** are about 3 mm. long by 2 mm. broad, the macula of the saccule being a little narrower (1.5–1.6 mm.) than those of the utricle (2 mm.). At the margin of these areas the cells are at first cuboidal, next low columnar, and then abruptly increase in length, until they measure from 30–35 μ, in contrast with their usual height of from 3–4 μ. The special area includes two kinds of elements, the sustentacular cells and the hair-cells. The **sustentacular cells** are long, rather narrow, irregularly cylindrical elements and extend the entire thickness of the epithelial layer,

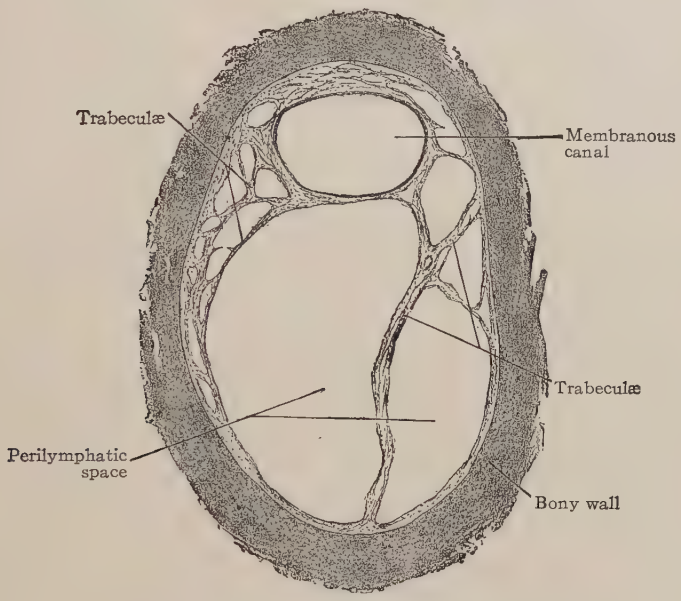


FIG. 411—Transverse section of superior semicircular canal, showing relations of membranous to bony tube. × 35.

resting upon a well-developed basement-membrane by their expanded or divided basal processes. They present a swelling enclosing an oval nucleus and terminate at the surface in a cuticular zone. The cylindrical **hair-cells** are broader and shorter than the sustentacular cells, and reach from the free surface only as far as the middle of the epithelial layer, where each cell terminates usually in a rounded or somewhat swollen end containing a spherical nucleus. The central end, next to the free surface, exhibits a differentiation into a cuticular zone, similar to that covering the inner ends of the sustentacular elements. From the free border of each hair-cell, a stiff robust hair (20–25 μ long) projects into the endolymph. This conical process, however, is resolvable into a number of agglutinated finer hairs or rods.

The free surface of the neuro-epithelium within the saccule and the utricle is covered by a remarkable structure, the so-called **otolith membrane.**

This consists of a gelatinous substance in which are embedded numberless small crystalline bodies, the **otoliths** or **ear-stones.** Between it and the cuticular zone is a space filled with endolymph, through which the hair-cells pass to the otolith membrane. The otoliths, also called **otoconia,** are minute crystals, usually hexagonal in form, with slightly rounded angles, and from 9–11 μ in length. They are composed of calcium carbonate with an organic basis.

On reaching the maculæ the nerve-fibres form a subepithelial plexus from which fine bundles of fibres pass towards the free surface. The fibres usually lose their myelin sheaths in passing through the basement membrane and then run between the sustentacular cells to about the middle of the epithelium. There they break up into fine fibrillæ, which surround the hair-cells.

The **cristæ staticæ** within the ampullæ of the semicircular canals have the form of ridge-like elevations, or crests, and are covered with neuro-epithelium similar to that of the maculæ. The hairs of the hair-cells, however, are longer. Otoliths are usually not present over the cristæ of the ampullæ.

The semicircular canals and their ampullæ, and the saccule and utricle with their otoliths are often termed collectively the vestibular apparatus, and have equilibrial functions. They are an important part of the mechanism by which we maintain a definite orientation with reference to the lines of gravitational force. These organs are especially large in fishes and birds —animals which are often out of contact with solid ground. They are readily seen in cartilaginous and bony fishes, in which they are easily dissected.

FIG. 412—Crista statica.

The Cochlear Duct.—The membranous cochlea, or **ductus cochlearis,** lies within the bony cochlea and like it includes from two and one-half to two and three-quarter turns, named respectively the **basal, middle,** and **apical,** the latter being three fourths of a turn at the apex of the cochlea. The **basilar membrane,** or **membranous spiral lamina** extends from the free border of the lamina spiralis ossea to the outer wall of the cochlea, where it is connected to an inward bulging of the periosteum and subperiosteal tissue, called the **spiral ligament.** The space below is the **scala tympani** and communicates, in the macerated skull, with the tympanum through the round window. **Reissner's membrane** extends from the upper surface of the osseous lamina near its outer end, obliquely upwards and outwards, to the external wall of the cochlea. The compartment above this membrane is the **scala vestibuli** and communicates with the perilymphatic space of the vestibule. The scalæ tympani and vestibuli communicate only at the apex of the cochlea through the helicotrema. They are lined by a delicate fibrous periosteum, usually covered on the surface which is in contact with the enclosed perilymph by a single layer of endothelial plates.

The middle compartment, the ductus cochlearis, is triangular on cross-section (Fig. 413).

Architecture and Structure of the Cochlear Duct.—**Reissner's membrane,** or **membrana vestibularis,** the delicate partition separating the cochlear duct from the scala vestibuli, begins on the upper surface of the lamina spiralis, about .2 mm. medial to the free edge of the bony shelf, and extends at an angle of from 40–45° with the lamina spiralis ossea to the outer wall of the cochlea, where it is attached to the periosteum. Notwithstanding its excessive thinness it consists of three layers: (**a**) a very delicate middle **stratum of connective tissue,** (**b**) the **endothelium** covering the vestibular side, and (**c**) the **epithelium** derived from the ectodermic cochlear duct. It also contains sparingly distributed capillary blood-vessels.

The **outer wall** of the cochlear duct (Fig. 414) is bounded by a part of

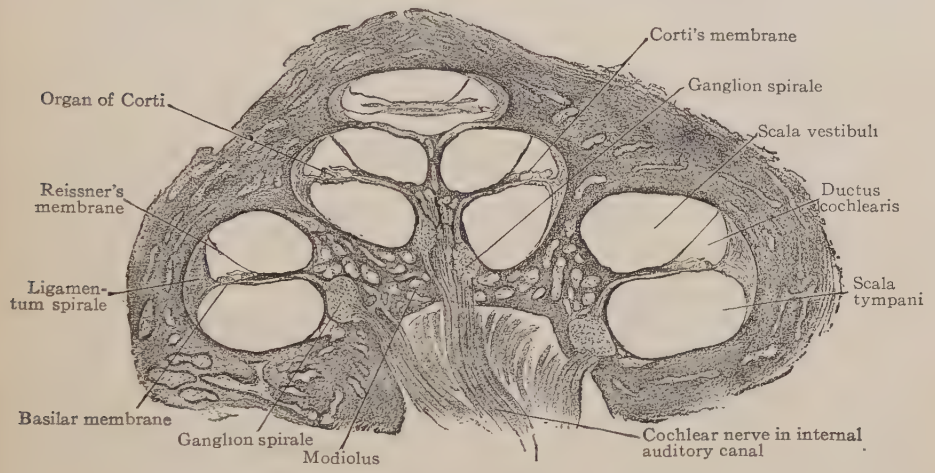


FIG. 413—Section of human cochlea passing through axis of modiolus. × 12.

a thickened crescentic cushion of connective tissue, whose convex surface is closely united with the bony wall and whose generally concave surface looks towards the cochlear duct. This structure, the **ligamentum spirale,** extends slightly above the attachment of Reissner's membrane and to a greater distance below the attachment of the basilar membrane, thus forming part of the outer walls of the scalæ vestibuli and tympani. At its junction with the basilar membrane it presents a marked projection, the **crista basilaris,** while a very slight elevation marks the point of attachment of the membrane of Reissner. The part of this ligament lying between these projections corresponds to the outer wall of the cochlear duct. Its concave free inner surface is broken by a third elevation, the **prominentia spiralis,** or **accessory spiral ligament,** distinguished usually by the presence of one large (**vas prominens**) or several small blood-vessels. The lower and smaller of these two divisions of the outer wall is called the **sulcus spiralis externus** and is lined by cuboidal epithelium, while the larger upper division is occupied by a peculiar vascular structure, the **stria vascularis,** which contains

capillary blood-vessels between its epithelial cells. This is probably the site of formation of the endolymph.

The **ligamentum spiralis** is composed of a peculiar connective tissue, rich in cells and blood-vessels. Its thin outer layer forms the periosteum and is denser than the adjacent loose connective tissue. The latter is broadest opposite the scala tympani, where its fibres converge towards the crista basilaris.

The **tympanic wall,** or **floor** of the cochlear duct, (Fig. 414) comprises the **basilar membrane,** extending from the basilar crest to the outer end of the bony spiral lamina, and the **limbus laminæ spiralis,** which includes this wall from the attachment of Reissner's membrane to the end of the bony lamina. The limbus or **crista spiralis** is a thick mass of connective tissue upon the

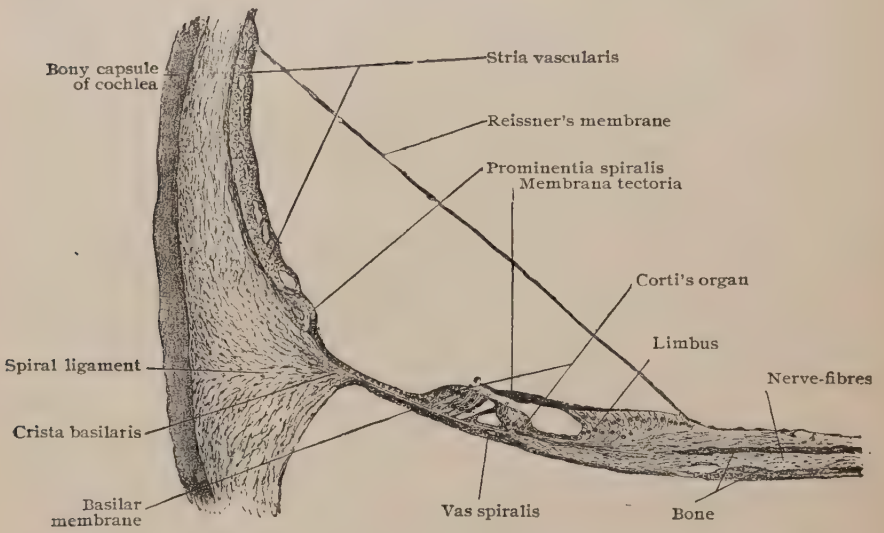


FIG. 414—Part of section of human cochlea, showing cochlear duct with Corti's organ. × 90. (*Preparation by Dr. Ralph Butler.*)

upper surface of the outer end of the osseous lamina spiralis. Its outer extremity is deeply grooved to form a gutter, the **sulcus spiralis internus,** the projections of the limbus above and below the sulcus forming respectively its **superior** (vestibular) and **inferior** (tympanic) **labia.** The lower lip is continuous externally with the basilar membrane and is perforated near its outer end by some 4000 apertures (**foramina nervosa**) transmitting minute branches of the cochlear nerve. The epithelium of the sulcus spiralis internus consists of a single layer of low cuboidal or flattened cells, continuous with the highly specialized elements of Corti's organ below.

The **basilar membrane** consists of a median (inner) and a lateral (outer) part. The former (**zona arcuata**) is thin and supports the modified neuro-epithelium constituting the organ of Corti; the outer part (**zona pectinata**) is the thicker division and lies external to the foot-plates of the outer rods of Corti. The basilar membrane is made up of three distinct layers—the

epithelium, the substantia propria, and the tympanic lamella. The **substantia propria** is formed of an almost homogeneous connective tissue with a few nuclei and fine fibres, which radiate towards the outer edge of the spiral lamina. The **tympanic lamella** contains numbers of fusiform cells of immature character interspersed with fibres. In this location the differentiation of the mesodermic cells lining the tympanic canal has never advanced to the production of typical endothelial plates, the free surface of the lamella being invested by the short fusiform cells alone. The inner zone of this layer contains capillaries which empty into one, or sometimes two, veins, frequently seen under the tunnel of Corti and known as the **vas spirale.** The **epithelium** covering the inner zone of the basilar membrane forms the organ of Corti, a conspicuous example of specialization of neuro-epithelium.

The Organ of Corti.—The organ of Corti, or **organon spirale,** con-

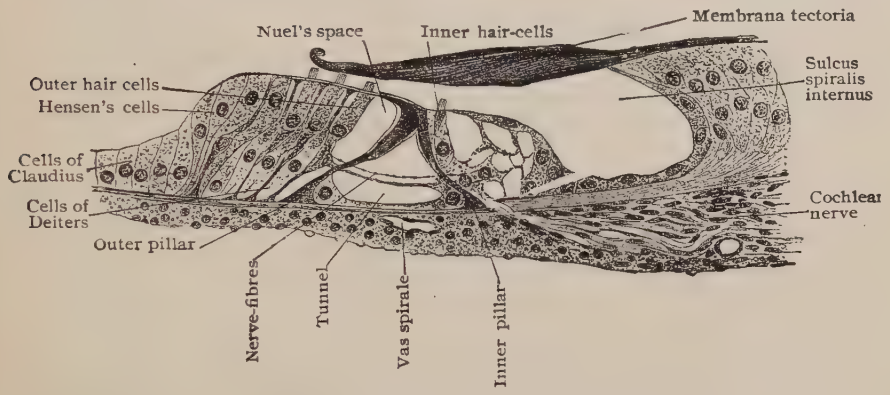


FIG. 415—Section showing details of Corti's organ from human cochlea; section is slightly oblique, hence width is somewhat exaggerated. × 375. (*Preparation by Dr. Ralph Buller*)

sists in a general way of a series of epithelial arches formed by the interlocking of the upper ends of converging and greatly modified epithelial cells, the **pillars**, or **rods, of Corti,** upon the inner and outer sides of which rest groups of the **auditory** neuro-epithelial elements, and the **sustentacular cells.** The triangular space included between the converging pillars of Corti above and the basilar membrane below constitutes the **tunnel of Corti,** which is, therefore, only an intercellular space of unusual size. It contains probably a soft semi-fluid intercellular substance serving to support the nerve-fibrils traversing the space (Fig. 415). The **pillars of Corti,** examined in detail, prove to be composed of two parts the denser substance of the pillar proper, and a thin, imperfect protoplasmic envelope. This presents, at the base directed towards the cavity of the tunnel, a triangular expansion, which contains the nucleus. Each pillar possesses a slender slightly sigmoid, longitudinally striated **body,** whose upper end terminates in a triangular **head,** and whose lower extremity expands into the **foot** resting upon the basilar membrane. The inner pillar is shorter, more

perpendicular, and less curved than the outer. The inner pillars are more numerous but narrower than the outer elements, from which arrangement it follows that the broader outer rods articulate with two and sometimes three of the inner pillars, the number of the latter in man being estimated by Retzius at 5600, as against 3850 of the outer rods.

Immediately medial to the arch of Corti, resting upon the inner rods, a single row of specialized epithelial elements extends as the **inner auditory** or **hair-cells.** These elements extending in length little more than the outer half of the epithelial layer possess a columnar body containing an oval nucleus. The outer somewhat constricted end of each hair-cell is limited by a sharply defined cuticular zone, from the free surface of which project in man, some twenty-five **hairs.** The inner hair-cells are less numerous (according to Retzius about 3500), as well as shorter and broader, than the corresponding outer elements. Their relation to the inner rods of Corti is such, that to every three rods two hair-cells are applied. The **inner sustentacular cells** lie below the inner hair-cells and are continuous with the lower cells of the sulcus spiralis.

The cells covering the basilar membrane from the outer pillar to the basilar crest comprise three groups: (a) those composing the outer part of Corti's organ, including the **outer hair-cells** and **cells of Deiters;** (b) the **outer sustentacular cells,** or **cells of Hensen;** (c) and the low cuboidal elements, the **cells of Claudius,** investing the outermost part of the basilar membrane.

The **outer auditory** or **hair-cells** are about five times more numerous (approximately 18,000 according to Waldeyer) than the corresponding inner elements, and in man and apes are disposed in three or four rows. They alternate with the peculiar end-plates, or "phalanges," of Deiters' cells, which separate the ends of the hair-cells and join to form a cuticular meshwork, the **membrana reticularis,** through the openings of which the hair-cells reach the free surface. The inner row of these hair-cells lies directly upon the outer rods of Corti, so placed that each cell, as a rule, rests upon the adjoining halves of two rods. The cells of the second row, however, are so disposed that each cell lies opposite a single rod, whilst the third layer repeats the arrangement of the first. In consequence of this grouping, these elements, in conjunction with the phalanges, appear in surface views like a checker-board mosaic, in which the oval free ends of the auditory cells are included between the peculiar compressed and indented octagonal areas of the end-plates of Deiters' cells (Fig. 416). The outer hair-cells are cylindrical in their general form, terminating about the middle of the epithelial layer in slightly expanded rounded ends, near which the spherical nuclei are situated. The outer sharply defined ends of the cells are distinguished by a cuticular border supporting about twenty-five rigid auditory rods or hairs which project beyond the level of the membrana reticularis.

The cells of Deiters have much in common with the rods of Corti, like these being specialized sustentacular epithelial cells which extend the entire thickness of the epithelial stratum to terminate in the peculiar end-plates, or phalanges. It follows, that while the free surface of Corti's organ is

composed of both auditory and sustentacular cells, the elements resting upon the basilar membrane are of one kind alone—the cells of Deiters. The bodies of the latter consist of two parts, the elongated cylindrical **chief portion** of the cell, containing the spherical nucleus and resting upon the basilar membrane, and the greatly attenuated pyramidal **phalangeal process.** A system of communicating intercellular clefts, the **spaces of Nuel,** lie between the auditory and supporting cells; like the tunnel of Corti, these spaces are occupied by a semi-fluid intercellular substance. The cells of Deiters are arranged, as a rule, in three rows, although in places within the upper turns four or even five alternating rows are sometimes found. Each cell contains a fine condensed filament, the **fibre of Retzius,** which begins near the middle of the base with a conical expansion and extends through the cell-body to the apex of the phalangeal process.

The **membrana tectoria,** or **Corti's membrane,** stretches laterally from

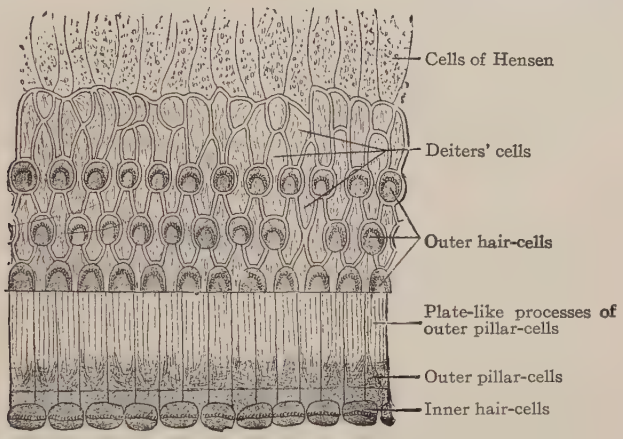


FIG. 416—Corti's organ viewed from above, showing mosaic formed by pillars and Deiters' cells; outer ends of auditory cells occupy meshes of cuticular network. (*Retzius*)

the upper lip of the limbus, above the sulcus spiralis and Corti's organ, as far as the last row of outer hair-cells. The membrane is a cuticular production, formed originally by the epithelial cells covering the adjacent region of the limbus. Medially it rests upon the epithelial cells from which it projects outwards above the organ of Corti. The membrane seems to be composed of fine resistant fibres, held together by an interfibrillar substance. During life the membrane is probably soft and gelatinous, and much less rigid than its appearance indicates after the effect of reagents.

The **outer sustentacular cells,** or **cells of Hensen,** form a zone immediately external to the last Deiters' cells. These elements resemble the inner sustentacular cells, but differ somewhat in form and arrangement. In consequence of their oblique position, the bodies are not only greatly elongated, but also imbricated. The **cells of Claudius** are the direct continuations of Hensen's cells, and laterally pass uninterruptedly into the low columnar elements covering the remaining part of the basilar membrane. They

consist of a single row of cuboidal cells possessing clear, faintly granular protoplasm and spherical nuclei.

Ductus endolymphaticus.—This is a slender tube which begins at the utriculo-saccular canal and traverses the narrow bony canal—the aqueductus vestibuli—to end in an enlargement, the **saccus endolymphaticus,** beneath the dura mater of the posterior surface of the petrous portion of the temporal bone. The duct is lined with flat epithelium, while in the saccus is a region showing crypt-like irregularities and lined with columnar epithelium. The drainage of the endolymph from the ductus cochlearis is probably by way of the canalis reuniens, sacculus, ductus endolymphaticus to the saccus endolymphaticus, from which it passes through the walls of columnar-lined crypts into adjacent vascular plexuses (Guild).

The Nerves of the Membranous Labyrinth.—The branches of the **cochlear division** of the eighth nerve enter the base of the cochlea through numerous small foramina, those destined for the apical turn traversing the central canal of the modiolus. From the modiolus a series of lateral branches diverge at regular intervals through canals which communicate with the peripheral spiral canal. Within the peripheral canal the nerve-fibres join numerous aggregations of bipolar nerve-cells, which continue along the spiral canal and collectively constitute the **ganglion spirale.** From these cells dendrites are given off, which pass along the canals within the spiral lamina to its margin, to enter the epithelial layer close to the inner rod of Corti. The radiating bundles pass within the epithelium to the mesial side of the base of the inner pillar; here they divide into two sets of fibrillæ, one, the **mesial spiral fasciculus,** going to the inner hair-cells and the other the **lateral spiral fasciculus,** passing between the inner pillars to reach the tunnel of Corti. Of the fibrillæ of the lateral fasciculus some extend between the outer pillar of Corti and the first rows of hair-cells, whilst others course between the rows of Deiters' cells to reach the remaining hair-cells.

The nerves supplying the saccule, utricle, and the semicircular canals are all fibres from the **vestibular division** of the eighth nerve. They traverse the bony labyrinth through canals that open internally at certain areas, the **maculæ cribrosæ,** in close relation to the specialized areas in the wall of the membranous labyrinth. The relations of the nerve fibres to the receptive cells of these maculæ and cristæ have been described.

Blood-Vessels of the Membranous Labyrinth.—The auditory artery, a branch of the basilar, after entering the internal auditory meatus divides into three branches (1) the **vestibular artery** accompanies the utriculo-ampullary nerve and supplies the upper part of the vestibule, including the posterior part of the utricle with its macula, the saccule, and the cristæ of the upper and outer ampullæ of the corresponding semicircular canals. (2) The **cochlear artery** pursues a spiral course. It gives off three branches, two of which are distributed to the lower turn of the cochlea, while the third supplies the middle and apical turns. (3) The **vestibulo-cochlear artery** arises either from the cochlear artery or independently and divides, within the spiral lamina, into a cochlear and a vestibular branch. The **cochlear branch** is distributed to the lower turn of the cochlea and anastomoses with the cochlear artery proper. The **vestibular branch** is distributed to the lower part of the vestibule, including the lower part

of the saccule and utricle, to the crus commune and part of the semicircular canals, and to the lower end of the cochlea. The macula of the saccule receives its arterial supply from a blood-vessel which usually arises from the common stem of the vestibulo-cochlear artery, or, more rarely, runs independently through the whole internal meatus. A similar origin applies to the artery supplying the nerve of the posterior ampulla. In the base of the spiral lamina the arteries are connected by capillary loops especially in the lower turn of the cochlea. One or more spiral vessels are often seen under the tunnel of Corti within the tympanic covering of the basilar membrane. The region of the stria vascularis and prominentia spiralis is especially well supplied with blood-vessels. Those seen in the scala tympani are principally veins, while a larger number of arteries are found in the scala vestibuli. The blood-supply of the lower turn of the cochlea is much more generous than that of the others.

The **veins** from the cochlea include: (1) the vein which collects the blood from the semicircular canals; (2) the vein which collects from the whole cochlear canal through the anterior, posterior, and middle spiral veins and from most of the vestibule through the anterior and posterior vestibular veins; and (3) the venous plexus of the inner auditory canal, which receives the large central cochlear vein.

THE NOSE

Although only a small part of the nasal chambers is occupied by the peripheral olfactory organ in man, the greater part forming the beginning of the respiratory tract, comparative anatomy and embryology establish the primary significance of the nasal groove, and its derivations as the organ of smell, the relation of the nose to respiration being entirely secondary. The nose, therefore, is appropriately grouped with the organs of special sense.

The nose is conventionally divided into two portions: the **external nose,** consisting of a framework of bone, cartilage, and fibrous tissue, which insures the maintenance of apertures for the passage of air, and the **nasal chamber,** divided by a septum into the right and left **nasal fossæ** and lined by mucous membrane. The junction of the latter with the skin is marked by a limiting ridge, the **limen vestibuli,** on the inner surface of the vestibule, a short distance above the nostril. Apart from the unusually large sebaceous glands surrounding and the hairs (**vibrissæ**) guarding the nares, the external nose presents little of especial histological interest. The description of the external nose and of the complicated modelling of the nasal fossæ fall within the province of gross anatomy. The present consideration of the nose, therefore, may be limited to the mucous membrane lining the nasal chamber.

THE NASAL MUCOUS MEMBRANE

Beyond the limit of the integument clothing the vestibule, the nasal fossa is lined by mucous membrane continuous with that of the nasopharynx through the choanæ. Since, in addition, to lining the tract over which the respired air passes, the nasal mucous membrane contains the cells

receiving the impressions giving rise to the sensation of smell, it is appropriately divided into a **respiratory** and an **olfactory** part.

The Olfactory Region.—The highly specialized regio olfactoria is quite limited in extent and embraces an area situated over the upper and adjoining part of the middle turbinate and the corresponding part of the septum. In fresh preparations the olfactory area usually, but not always, can be approximately mapped out by the yellowish hue, lighter or darker, that distinguishes it from the respiratory region in which the mucous membrane exhibits a rosy tint.

The **epithelium** contains two chief constituents—the supporting and the olfactory cells. The **supporting cells** are tall cylindrical elements, about 60 μ in height, that extend the entire thickness of the epithelium.

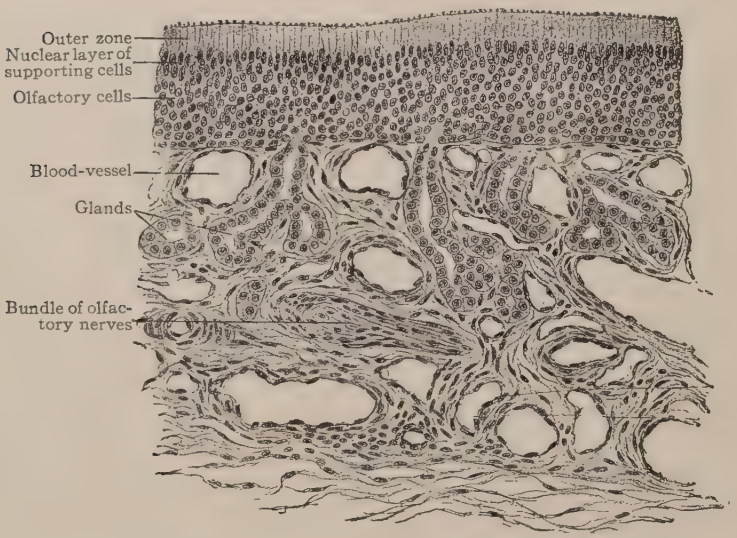


FIG. 417—Section of olfactory mucous membrane. × 300.

Their outer and broader ends are of uniform width and contain the oval nuclei which, lying approximately at the same line and staining readily, form a deeply colored and conspicuous nuclear stratum at some distance beneath the free margin. Between the latter and the row of nuclei, the epithelium presents a clear zone devoid of nuclei. The inner part of the supporting cells is thinner and irregular in contour and often terminates by splitting into two or more basal processes that rest upon the tunica propria. Between these ends lie smaller pyramidal elements, the **basal cells,** that probably represent younger and supplementary forms of the sustentacular cells. The granular protoplasm of the basal processes often contains pigment particles.

The **olfactory cells,** the perceptive elements receiving the smell-stimuli, consist of a fusiform cell-body lodging a spherical nucleus and two attenuated processes, a peripheral and a central. The olfactory cells are

in fact sensory neurones that have retained their primitive position within the surface epithelium, as in many invertebrates, instead of receding, as is usual in the higher animals, to situations more remote from the exterior. The slender peripheral process of the olfactory cell, which corresponds to the dendrite of the neurone, is of uniform thickness and ends at the surface in a small hemispherical knob that projects slightly beyond the general level of the epithelium and bears from 6–8 minute stiff cilia, the **olfactory hairs.** The length of the peripheral processes varies, since the cell-bodies occupy different levels within the epithelium in order to accommodate their great number. The central processes of the olfactory cells, much more delicate than the peripheral are directly continued as the subjacent unmyelinated nerve-fibres within the tunica propria, which pass through the cribriform plate of the ethmoid to enter the brain and end in the arborizations within the olfactory glomeruli of the bulbus olfactorius.

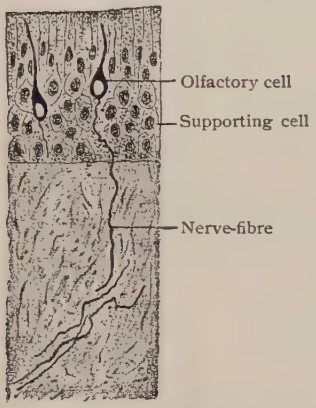


FIG. 418—Section of olfactory mucous membrane, silver preparation; two olfactory cells are seen, one sending nerve-fibre towards the brain. × 335. (*Brunn.*)

The **tunica propria** is differentiated into a superficial and a deep layer by the lymphoid character of the stratum directly beneath the epithelium. The superficial layer, from 15–20 μ thick, consists of closely packed irregularly round cells, resembling lymphocytes and meagre bundles of delicate connective tissue. The deep layer, on the other hand, contains robust bundles of fibro-elastic tissue and relatively few cells. A distinct membrana propria is wanting within the olfactory region.

FIG. 419—Isolated elements of epithelium of olfactory mucous membrane; *a*, olfactory cells; *b*, supporting cells. × 600. (*Brunn.*)

The **olfactory glands,** or **glands of Bowman,** are characteristic of the olfactory region and elaborate a thin and watery secretion. They open onto the free surface by very narrow ducts that lead into saccular fusiform dilatations, the **ampullæ,** into which the tubular alveoli pass. The ducts possess an independent lining of flattened cells, that extend as far as the surface and lie between the surrounding epithelial elements. The dilatations are clothed with flattened or low cuboidal cells, which are replaced by those of irregular columnar or pyramidal form, often pigmented, within the tubular

alveoli. From the character of their secretion, the glands of Bowman are probably to be reckoned as serous and not mucous.

The Respiratory Region.—The mucous membrane lining the respiratory region differs greatly in thickness in various parts of the nasal fossa. In situations where the contained cavernous tissue is well represented, as over the inferior turbinate, it may reach a thickness of several millimeters, while when such tissue is wanting, as on the lateral wall, it is reduced to less than a millimeter.

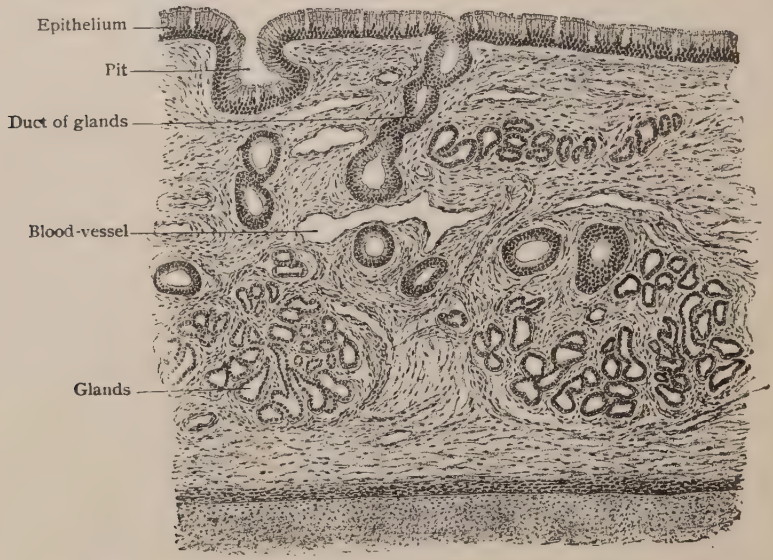


FIG. 420—Section of respiratory mucous membrane covering nasal septum. × 75.

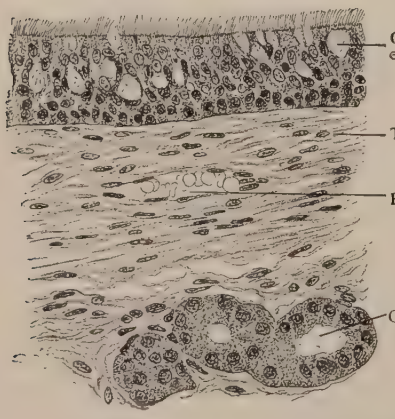


FIG. 421—Section of mucous membrane lining maxillary sinus. × 280. (*Preparation by Dr. J. P. Tunis.*)

The **epithelium** is stratified ciliated columnar in type, from 50–70 μ thick, and includes the tall ciliated surface cells, between whose inner ends lie the irregularly columnar basal cells. Numerous elements exhibit various stages of conversion into mucus-containing goblet-cells. The current produced by the cilia is towards the posterior nares. Intraepithelial migratory lymphocytes are also common. Beneath the epithelium stretches the membrana propria, varying greatly in thickness; although in certain localities feebly developed, it is usually well marked and measures

from 2–10 μ. Under pathological conditions its thickness may increase fourfold or more. In many places the membrana propria is pierced by minute vertical channels, the **basal canals,** in which connective tissue cells and leucocytes are found.

The **tunica propria** consists of interlacing bundles of fibro-elastic tissue

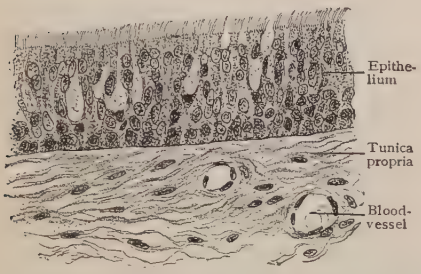


FIG. 422—Section of mucous membrane lining frontal sinus. × 280. (*Preparation by Dr. J. P. Tunis.*)

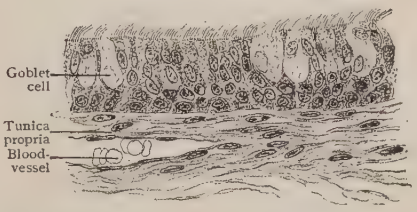


FIG. 423—Section of mucous membrane lining sphenoidal sinus. × 280. (*Preparation by Dr. J. P. Tunis.*)

which are most compactly disposed towards the subjacent periosteum. The looser superficial stratum is rich in cells and here and there contains aggregations of lymphocytes that may be regarded as masses of adenoid tissue. In certain parts of the nasal fossæ, the stroma of the mucous membrane contains vascular areas composed of numerous intercommunicating blood-spaces that confer the character of a true cavernous tissue. These specialized areas, the **corpora cavernosa,** as they are called, are especially well developed over the inferior and the lower margin and posterior extremity of the middle turbinate, much less so over the posterior end of the upper turbinate. Where typical, they occupy practically the entire thickness of the mucous membrane from periosteum to epithelium, the interlacunar trabeculæ containing the glands and blood-vessels destined for the subepithelial stroma. The blood-sinuses include a superficial reticular zone of smaller spaces and a deeper one of larger lacunæ.

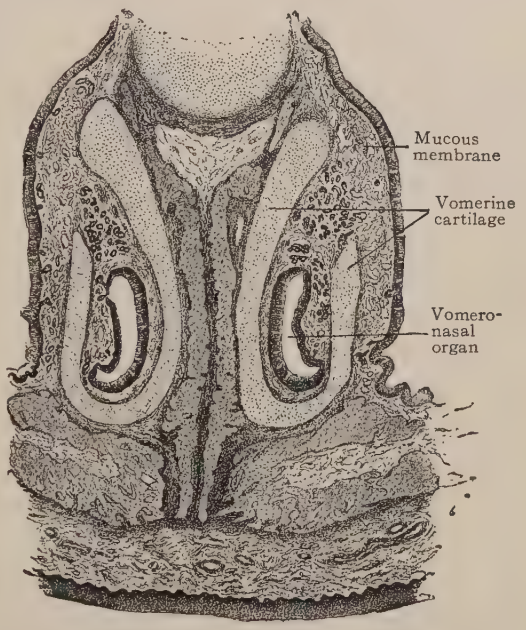


FIG. 424—Part of frontal section through nasal fossæ of kitten, showing vomeronasal organs. × 20.

The **glands** of the respiratory region are very numerous, although varying in size, tubo-alveolar in form and, for the most part, mixed mucous

in type. The chief ducts open on the free surface by minute orifices barely distinguishable with the unaided eye. Their deeper ends branch irregularly into tubes that bear the ovoid terminal alveoli. The latter are lined with mucus-secreting cells, between which lie the crescentic groups of serous cells that stamp the glands as mixed. In exceptional cases exclusively serous glands are also encountered.

The nasal fossæ communicate with a number of remarkable cavities, the **accessory air-spaces,** hollowed out within the surrounding bones, which are filled with air and lined by mucous membrane directly continuous with that of the meatuses. These pneumatic spaces include the **maxillary,** the **frontal,** and the **sphenoidal sinuses,** and the **ethmoidal air-cells,** all paired and within the corresponding bones. The mucous membrane lining these spaces resembles in general that of the adjoining nasal fossæ, but is very much thinner. It includes a stratified ciliated columnar epithelium, invaded by numerous lymphoid cells, a delicate basement membrane and a tunica propria poor in elastic fibres and inseparably blended with the periosteum of which, in fact, it is part. Small scattered mucous glands occur in meagre numbers in the maxillary sinus, being most plentiful in the vicinity of the opening into the nasal fossa.

Vomeronasal Organ.—Mention should be made of the rudimentary structure found in man, almost constantly in the new-born child and sometimes in the adult, as a representative of the vomeronasal organ, or organ of Jacobson, that is present, in varying degrees of perfection, in all amniotic vertebrates. In many animals possessing in high degree the sense of smell, the organ is well developed and continues to grow throughout life, but its exact function is still undetermined.

In man the organ is represented by a laterally compressed tubular diverticulum from the septal mucous membrane from 1.5–6 mm. in length, that passes backwards to end blindly beneath the mucous membrane on each side of the nasal septum. The median wall of the diverticulum is clothed with tall columnar cells resembling those of the olfactory region. The epithelium covering of the lateral wall corresponds to that of the respiratory organ. In many animals branches of the vomeronasal nerve are traceable to Jacobson's organ. These pass to the ganglion of the vomeronasal nerve, and from the ganglion the afferent axones enter the accessory olfactory bulb.

THE TASTE BUDS

In the description of the tongue and its papillæ, reference was made to the presence of specialized epithelial structures, the **taste-buds,** that serve for the reception of gustatory stimuli. These bodies collectively constitute the peripheral sense-organ of taste and as such will be here considered.

As implied by their name, the taste-buds, or **calyculi gustatorii,** are irregular ellipsoidal or conical bodies, sometimes broadly oval but more often slender in outline, and in the adult measure from 70–80 μ in length and about half as much in breadth. Since they lie entirely within the stratified squamous epithelium clothing the mucous membrane, the necessary access

to the interior of the buds is afforded by minute **pore-channels,** each of which, beginning on the free surface at the **outer taste-pore,** leads through the intervening layer of epithelium to the **inner pore** that caps the subjacent

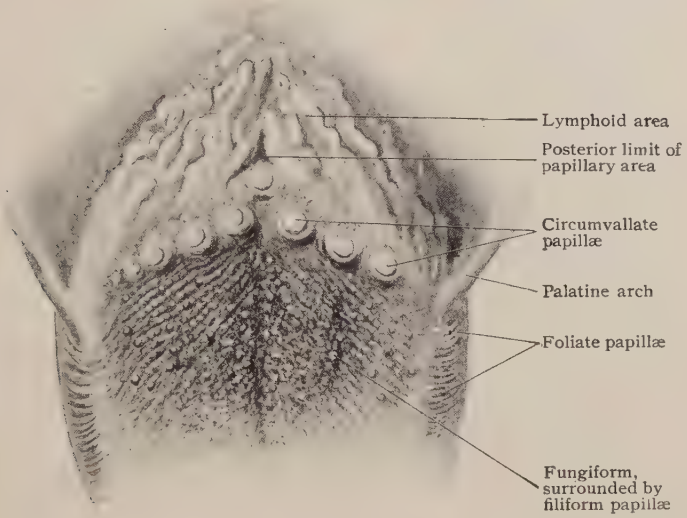


FIG. 425—Part of dorsum of the tongue, showing varieties of the papillæ; natural size.

pole of the bud. By means of these canals the sapid substances dissolved in the fluids of the mouth reach and impress the gustatory cells within the taste-buds. Pore-canals are not, however, invariably present, since, as

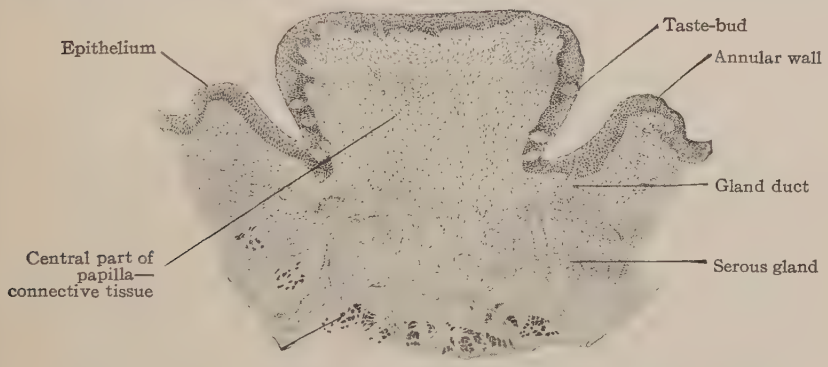


FIG. 426—Section across circumvallate papilla from child's tongue, showing central part and encircling wall. × 45.

pointed out by Graberg, certain taste-buds remain immature and retain their embryonal form and relations, being broad and conical and in contact with the free surface. In such buds the gustatory cells are few, only two or three, and so superficially placed that a distinct canal is absent. Occasionally double buds are encountered in which two gustatory bodies are

implanted by a common base, but partly retain their independence in having separate distal poles, each provided with its separate taste-pores and canal.

The chief position of the taste-buds is within the epithelium lining the sides of the annular groove on the circumvallate papillæ, the buds being more numerous and closely placed on the median than on the lateral wall of the furrow. Their number has been variously estimated, but it is probable that from 100 to 150 represents the maximum for a single papilla. The locality of next importance numerically is the papillæ foliatæ on the sides of the tongue in the furrows of which, even in man, the taste-buds are plentiful. Additional situations, in which, however, the taste-buds are very sparingly and uncertainly distributed, include the fungiform papillæ, the soft palate, the posterior surface of the epiglottis, and the mesial surface of the arytenoid cartilages. Within the fungiform papillæ a few buds may be found on the free surface where the epithelium is thinnest. Over the soft palate their distribution is irregular and uncertain, while in the larynx the buds are limited to the areas covered by squamous epithelium.

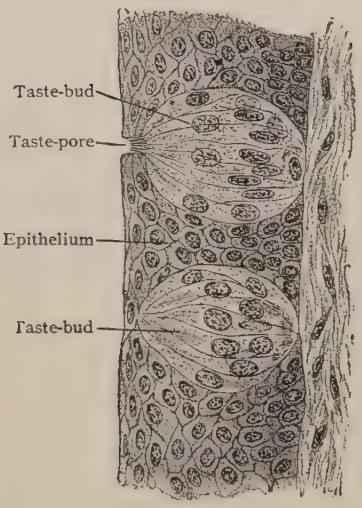


FIG. 427—Taste-buds in section; upper one shows gustatory hairs projecting into taste-pore. × 440.

Wherever found, the taste-buds consist exclusively of epithelial tissue and, in correspondence with other sense-organs, include two chief varieties of elements—the supporting cells and the highly specialized neuro-epithelium, the gustatory cells, among which lie the terminal fibrillæ of the nerves of taste.

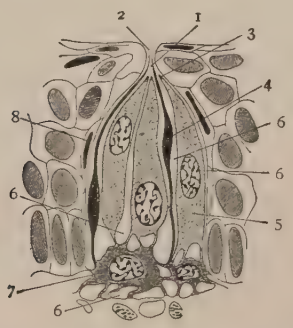


FIG. 428—Diagram illustrating architecture of taste-bud; 1, pore-canal; 2, 3, outer and inner taste-pores; 4, gustatory cell 5, supporting cell; 6, tissue-spaces: 7, basal cell; 8, sheath-cell. (*Graberg*)

FIG. 429—Partially separated cells of taste-bud with terminal filaments of gustatory nerve. × 510. (*Arnstein.*)

The **supporting cells** are represented principally by elongated epithelial elements that occupy both the superficial and deeper parts of the taste-buds of which they contribute the chief bulk. They vary in their individual contour, being lanceolate, wedge-shaped, or columnar, according to the modelling to which they are subjected by the neighboring cells. They possess large clear vesicular nuclei that contain little chromatin and, therefore, stain faintly. The position of the nucleus is inconstant, in some cells being near the base and in others in the middle or nearer the apex. The peripheral ends of the supporting cells, somewhat blunted and flattened and beset with a narrow cuticular zone, are closely grouped to bound the annular opening of the inner taste-pore, through which project the stiff hair-like processes of the gustatory cells. Their deeper, or central ends, are prolonged into one or more protoplasmic processes which unite with similar extensions of the basal cells, as the peculiar supporting cells at the base of the bud are called. The **basal cells** are modified sustentacular elements, probably epithelial in nature, which occupy the lower fourth of the buds, resting upon the subjacent epithelium, and, in turn, affording support for the elongated cells. Although differing in size and details of form, the basal cells are provided with oval nuclei and are generally more or less branched.

The **gustatory cells** are irregularly arranged between the more deeply placed supporting cells and enclosed within a shell formed by the more superficial ones. They are long and fusiform, reaching from the base of the bud to the inner taste-pore, through which the stiff hair-like processes that cap their outer ends project. Their slender nuclei, rich in chromatin and deeply staining, occupy the thickest parts of the cells, which beyond the nucleus are continued in either direction as thin processes. The peripheral ones, as noted, extend not only as far as the inner taste-pore, but through the latter and into the canal by means of the gustatory hairs into which the taste-cells are prolonged. The centrally directed ends are usually much the shorter and join the processes of the basal cells. The number of gustatory cells within a single taste-bud varies, in exceptional cases only two or three being present, but more often they are almost as numerous as the supporting cells.

The **nerves** distributed to the gustatory bodies are fibres of the seventh, ninth, and tenth nerves. From the rich subepithelial plexus numerous twigs ascend into the epithelium going directly into the basal pole of the taste-buds as the **intrabulbar fibres.** There are usually from two to five for each bud and on gaining the interior of the latter they undergo rapid division. A majority of the resulting fibrillæ ascend in tortuous windings towards the apex of the bud in the vicinity of which some end, while others recurve and end at lower levels. The fibrillæ terminate in free, usually minute knob-like endings, that lie between and in close contact with the supporting and gustatory cells. It is probable that in no instance do the nerve-fibrillæ actually unite with the gustatory cells, the relation being one of apposition and not of continuity.

APPENDIX

METHODS OF STUDY OF LIVING CELLS

TISSUE CULTURES IN VITRO

The growing of metazoan tissues outside the body in hanging drops or in modified Petri dishes is a comparatively recent thing. In 1897 Leo Loeb first published some observations on cells moving about outside the body in preparations of blood coagulum and agar. Harrison in 1907 was the first to describe his technic and gave figures showing the regeneration of nerve fibres taken from the frog embryo and grown in frog lymph in vitro. Since then scientists working in Europe and America have done a large amount of work. The papers on tissue culture have become so numerous that in 1925 Frl. Erdmann established a special journal for their publication in Berlin.

The embryo chick has been extensively used in tissue culture work. It is easy to obtain, inexpensive, and its age readily controlled. As the work progressed, two methods of culturing have developed. The Harrison-Carrel method uses for culture medium equal volumes of chick plasma and chick embryo extract. The Lewises use Locke–Lewis which is made up of 85 cc. of Locke's solution, 15 cc. of chicken bouillon and 0.25 gram of dextrose.

In working out the technic of culturing, three things were found to be necessary. First, the cells must have some supporting structure. For this the various workers have used spider web, cotton and silk fibres, fibrin, and the surface of the cover glass itself. The second requirement is a growth promoting substance found in largest quantities in embryonic tissue juice. Cells live a short time, perhaps 10–15 days without this substance, but for long continued culturing it is found to be absolutely necessary. The third essential is cell contact. Pure lines can not be started from one isolated cell. There must be several cells present in contact with each other if the culture is to flourish.

The hanging drop method is the one usually employed. The work is done aseptically. The embryonic chick—usually 7 or 8 days old—is removed with sterile forceps from the egg and opened in a small Petri dish containing sterile Locke-Lewis or Ringer's solution. The tissues to be studied are then transferred to other Petri dishes containing Locke–Lewis or Ringer's solution. Here they are cut up into small pieces about one mm. in diameter and transferred by means of a sterile pipette to a cover glass. In the Lewis method only a small amount of the solution is left on the cover glass. The cover glass is then inverted over a hard vaseline ring on a depression slide, and the culture is incubated at from 37–40° C. If the Harrison-Carrel method is used a drop of the embryonic tissue juice and a drop of the chick plasma are mixed on the cover glass and allowed to partly coagulate. The piece of tissue to be grown is then taken from the Petri dish and put on this coagulated drop, and the cover glass inverted over a depression slide and sealed with vaseline.

Often in less than 24 hours, the cells begin to migrate out from the explanted tissue. This migration depends on many things: among others

on the age of the embryo from which the tissue was taken; on the concentration of the various substances in the culture media; and on the temperature of the incubator. The cells will continue to migrate for days and divide by mitosis. In Locke-Lewis the usual life of the cultures varies from four to ten days—occasionally they live longer. In plasma-embryonic juice medium some tissues seem to live indefinitely. There is a strain of fibroblasts isolated from a chick embryo heart at the Rockefeller Institute which is still healthy and flourishing after thirteen years of cultivation in hanging drops. The transplants double themselves in size every 48 hours and are then cut into two pieces which are used to start new cultures. This process has been carried on for over 2330 generations. (June, 1926).

Many different kinds of cells have been cultured. Embryonic cells are easier to grow than cells from adult tissues, which migrate more slowly due no doubt to the greater consistency of the cytoplasm in the older tissues. The embryonic tissues which have been cultured are mesenchyme, endothelium, endoderm from the allantois, stomach, and intestine; ectoderm from the skin, amnion, iris, and retina; liver cells; involuntary, voluntary, and heart muscle cells, spleen cells, clasmotocytes, cartilage cells, and renal epithelium from the tubules. The adult tissues which have been cultured include ectoderm, connective tissue, spleen, lymph node, bone marrow, endothelium, thyroid, thymus, and cartilage cells.

Since tissue cultures lend themselves to the solution of a great variety of problems in bacteriology, histology, pathology, pharmacology, and physiology, it was soon realized that pure cultures, **i.e.** cells of one kind only, must be grown in order to interpret the results of the experiments accurately. At present pure cultures have been obtained of fibroblasts, cartilage cells, epithelium, and large mononuclear lymphocytes. These have been obtained either by taking the pure tissue from the organism as in the case of cartilage cells, though this is difficult to do as most tissues are complex and contain other cells as gland cells and amœboid cells; or they have been obtained by the survival of one kind of cell after the others have died out. This is the method used in obtaining the pure cultures of large mononuclears.

The different kinds of cells form characteristic growths as they migrate out from the explant. The fibroblasts form a reticular outgrowth, the cells at the edge being further apart and often apparently quite separate from the reticulum. The epithelial cells lining the intestine form a flat plate of closely adhering cells, while the voluntary muscle cells protrude from the explant as long multinucleate cells.

The culturing of tissues in hanging drops has greatly enhanced our knowledge of cell structure and of tissues. Here one can study the morphology of cell structure and of tissues. Here one can study the morphology of the individual cell, and notice the effect of vital dyes and of various physical and chemical agents upon it. At any moment the cells can be fixed and stained according to the usual histological methods and a permanent preparation obtained for comparison with the record of the living cell.

For a more detailed account of Tissue Culture and for a bibliography the reader is referred to Fischer's book on "Tissue Culture." and to the article by W. H. Lewis and M. R. Lewis "The Behavior of Cells in Tissue Culture" in Cowdry's "General Cytology."

MICRODISSECTION OF CELLS

The study of living cells by microdissection is being much used now, and with it remarkable discoveries have been made in regard to the nature of protoplasm and the inner structure of cells. Barber was the first to construct an instrument which could be readily used for this purpose though he used it chiefly for the isolation of single bacteria. Chambers* has recently invented a simpler apparatus which is much steadier and allows a wider range of work. It is composed essentially of three bars built up on each other and travelling in different directions, so that the needle which is clamped to the top bar can be moved in any of three dimensions. This apparatus is fastened to the stage of a compound microscope.

The cells to be studied are placed in a hanging drop in a moist chamber on the stage of the microscope. The moist chamber consists of a glass slide for the base, and three pieces of plate glass cemented together, as the sides with a cover glass for the top. One side of the chamber is left open for the entrance of the dissecting instrument. At the inner end of the chamber another piece of glass is cemented to form a trough for holding water. The sides of the chamber are lined with filter paper which dips into the water and so keeps the chamber moist.

The needles, or pipettes, to be used in the dissection are drawn out of hard or soft glass tubing to a very fine point. The end is bent at an acute angle so as to come up into the hanging drop on a slant. These glass needles are held rigidly in the apparatus which moves them steadily in any direction desired by the operator. Chambers uses this apparatus for the dissection of microscopic objects, for the injection of solutions and stains into cells, and for the withdrawal of parts of the cell, such as nuclei, chromosomes, and granules. There are almost limitless uses for this apparatus in the hands of a skilled worker.

SUPRAVITAL STAINING OF BLOOD

Within the last few years the supravital staining of blood has become very important. It has been largely used in the study of the origin of blood-cells, certain kinds of cells containing granules of one type or arrangement at one period of their history and other granules or a different arrangement of them at later periods. It has also been used in the study of blood in various pathological conditions.

The technic usually employed is very simple. It requires absolutely clean slides and cover slips, solutions of the vital dyes, salvoline, a compound microscope, and a warm box. The slides and cover slips are cleaned first in acid, sulphuric being generally used. They are left in this about three days. They are next washed in running water, hot water being preferred, for two or three hours, and care is taken that all the acid is removed from between the slides. They are then rinsed in distilled water and stored in 80 per cent. alcohol. When wanted for use, they are dried with a clean piece of cheese cloth and flamed.

The dyes generally used in blood-work are neutral red and Janus green, sometimes both are used together. In the case of neutral red, take 10 cc. of absolute alcohol and add to it 20–30 drops of a saturated solution of

*Chambers, R. New Apparatus and Methods for Dissection and Injection of Living Cells. Anat. Rec., vol. 24, 1922.

neutral red in absolute alcohol (Sabin, '23)*. The strength of the dye is determined by the color, a rose-red being desired. If the nuclei stain, it is too strong. If mitochondria are to be studied Sabin† adds three drops of a saturated solution of Janus green to 1 cc. of the above dilute neutral red solution. The slides are flooded with this stain and then placed in a vertical position so that any excess will drain off. When they are dry they can be stored until ready for use. In making the preparation for study, a drop of blood is put on a cover slip and inverted over the slide on which is the dried stain. The stain then gradually diffuses out into the plasma and the blood cells take it up. The cover slips are ringed with salvoline and studied in a warm box kept at 37° C.

Blood has been studied in hanging drops by W. H. and M. R. Lewis‡, in the following manner. Solutions of neutral red (1–5000) or Janus green (1–100,000) are made in a saline solution—preferably Locke solution. A hollow glass slide is ringed about the margin of the depression with salvoline. The drop of blood is put on an absolutely clean cover slip. A small drop of the stain is added by a sterile pipette. Any excess of liquid is withdrawn by the pipette and the cover glass preparation inverted over the hollow slide and studied in a warm box.

The warm box is essentially a wooden or asbestos box 18 inches long, 12 inches wide, 10 inches high at the back, and 5 inches high in front. The cover is in two parts which can be taken off to allow the placing of the microscope in the box. On the sides are sliding doors which give access for the operator's arms. There is a hole in the side or in the lid for a thermometer. The box is heated by an electric bulb which also serves as the source of illumination. A convenient type of bulb is a frosted Mazda lamp, 110 volts, 60 watts. In such a box, blood may be kept at body temperature for hours, and the movements of the cells observed.

USEFUL METHODS OF HISTOLOGICAL TECHNIC

With the exception of the fluid tissues, as blood and lymph scrapings from organs, as the spleen and the liver, or "teased" fragments separated with needles, as connective tissue or nerve-fibres, the tissues and organs of the body are so compact and opaque that very thin sections, made transparent by artificial means, are necessary for satisfactory microscopical examination. Moreover. in order to display the structural units, it is usually desirable to stain such sections with suitable dyes, so that advantage may be taken of the differences in the color affinity of the various parts of the cells or of the intercellular substances to secure adequate differentiation. After being stained, the sections are rendered transparent and enclosed in some mounting medium in which they may be preserved often for years without deterioration.

The methods devised or modified by the many engaged in histological work have resulted in the great mass of technical details described in the

*Sabin, F. R. Studies on Living Human Blood-Cells. Bull. Johns Hopkins Hosp., vol. 34, 1923.

†Cunningham, Sabin, Sugiyama, Kindwall. The Rôle of the Monocyte in Tuberculosis. Bull. Johns Hopkins Hosp., vol., 37, 1925.

‡Lewis, M. R. A Study of the Mononuclear of the Frog's Blood in Vitro. Arch. f. exp. Zellsforschung besonders Gewebezüchtung Explantation, Bd. II, 1925.

various books devoted to the subject. Here will be given a few procedures which may be depended upon to yield excellent results when properly carried out, and in the great majority of cases will be found to be adequate for the demonstration of structural details. The student undertaking such work for the first time is urged to persevere with the methods here given until he has repeatedly carried them to the successful results of which they are capable. Failures, sure to beset the beginner, should be carefully analyzed and be made to yield experience guarding against their repetition.

FROZEN SECTIONS OF FRESH TISSUES

Fresh tissue, the cells of which must be alive (i.e., if not kept in the ice chest, not more than two hours out of the body), in pieces not more than 2 × 10 × 10 mm., is frozen in dextrine solution, on the freezing microtome and cut in sections 5 to 15 microns thick.

Remove the sections from the knife with the tip of the finger and allow them to thaw thereon, thus avoiding later development of air bubbles.

Unroll the sections with camel's hair brush in 1 per cent. NaCl solution.

Stain 10 to 20 seconds in Unna's polychrome methylene blue.

Wash out momentarily in 1 per cent. NaCl solution.

Mount in Brun's glucose medium. Formula:—Glucose 240 cc., distilled water 840 cc., Spirits of Camphor, 60 cc., Glycerine 60 cc., filter.

Handle the sections from first salt solution through to the slide with a small glass rod-lifter. Keep the sections constantly moving while in the stain. The smaller the stain-cup the more readily tissue may be found in it if dropped from the lifter.

Formaldehyde-fixed material, first thoroughly washed in tap water, may be treated in exactly the same manner as fresh tissue. The color differentiation is materially different, but the process is of great convenience for the rapid examination of a great number of blocks from a given specimen, and the preparations may be kept permanently.

FIXATION AND PRESERVATION OF TISSUES

It is evident, that, no matter how carefully subsequent manipulations be conducted, unless the tissue itself be successfully preserved, the finished preparation will not present a trustworthy picture of the normal structure. The tissue must be secured, therefore, as fresh as possible, since in the case of delicate structures, as the epithelium lining the digestive canal, the post-mortem changes occurring within a few hours are sufficient to destroy interesting details. Tissues from the lower animals are readily obtained from the recently killed animal, while still warm and the cells yet alive; those from man are less easily secured, the early autopsy and some favorable operations being the usual sources for the histologist's stock. The manifest desideratum being to retain, as far as possible, structural details in the condition in which they existed during life, it is necessary to kill the tissue rapidly, otherwise all evidence of certain phases of cellular activity, as the figures of mitotic division, may disappear during the slow death of the cells.

This rapid killing of the tissues, known as **fixation,** is accomplished by plunging the fresh, preferably still warm, material into some suitable fixing solution. The solutions for this purpose are many, since some tissues fix well in certain fluids, while in the same ones other tissues may be only

indifferently preserved. The general precautions to be observed in fixing include; material should be in as small pieces as practicable, never over 2 cm. thick and better not more than half as much. Otherwise the penetration is incomplete with corresponding imperfect fixation. The volume of fixing fluid should be many (fifty or more) times that of the tissue. Further, the fluid should be changed whenever it becomes turbid. This often happens within the first few hours after the introduction of the tissue. The latter should not be washed in water on being removed from the animal, but placed in the fixing fluid directly, with the minimum handling and without being allowed to dry. A cushion of absorbent cotton affords desirable support and insures access of the reagent on all sides. Among the most useful fixing reagents are the following.

Zenker's Fluid.

Potassium bichromate	2.5 gm.
Sodium sulphate	1 gm.
Mercury bichloride	5 gm.
Distilled water, warm	100 cc.

Dissolve by heating and allow to cool. This stock solution keeps for a long time. **Just before using,** to each 20 cc. of the above solution, add 1 cc. of glacial acetic acid.

Place small pieces of tissue in a generous amount of the fluid for 10 to 24 hours; then wash in running water for 12 to 24 hours; transfer to 50 per cent. alcohol for several hours; then into 60, 70, and 90 per cent. alcohols, to which have been added a few drops of tincture of iodine, 6 to 12 hours in each. By the use of iodine is effected the removal of the mercuric chloride crystals which are deposited in the tissue; the pieces of tissue are then placed in 95 per cent. alcohol for 6 to 24 hours to remove the iodine. If one desires to keep the tissue for some time before embedding, it is transferred to 80 per cent. alcohol. The complete removal of mercuric chloride deposits is ensured by placing the cut sections, before staining, in 95 per cent. alcohol + iodine for 3 to 5 minutes, and then passing through clear 95 per cent. alcohol to remove traces of iodine.

This is a good fixative for routine work.

Helly's Modification of Zenker's Fluid: Formol-Zenker.

This is Zenker's fluid in which formaldehyde solution is used instead of glacial acetic acid. **Just before using,** add 5 parts of formaldehyde solution (full strength) to 95 parts of the stock solution of salts, as made up for Zenker's fluid. This is an excellent preservative of cytoplasmic granules in many types of cells. Fix for 6 hours. After-treatment as for Zenker's.

Tellyesnizcky's Fluid.

Potassium bichromate	3 gm.
Distilled water	100 cc.

Just before using add 5 cc. of glacial acetic acid.

Moderate sized pieces of tissue remain in the solution 18–24 hours; then are washed in running water 3–5 hours; and carried through 50, 70 and 95 alcohols, each for one day. This fluid is excellent for large embryos.

Müller's Fluid.

Potassium bichromate	25–30 gm.
Sodium sulphate	10 gm.
Water	1000 cc.

This classic fixing fluid requires prolonged action, from two to eight weeks or longer, and a large excess in proportion to the volume of the material. During the first week, the fluid should be changed daily, or in the beginning oftener if it becomes turbid; thereafter, each week. After a variable time, the tissue is washed in running water for 12–24 hours and then transferred to 70 per cent. alcohol and placed in the dark, with occasional renewal of the alcohol. If, however, the material be nervous tissue intended for subsequent treatment with special methods, such as Weigert staining, it is transferred, after slight rinsing, directly to the alcohol. This fluid although hardening evenly and without shrinkage large masses, as entire small brains and cords, has the disadvantage of being not only tedious, but also lacking in accurate nuclear fixation. Since, however, it is the basis of several combinations of value, its preparation as a stock solution is desirable.

Orth's Fluid, Formol—Müller.

Müller's fluid	100 cc.
Formalin (40 p.c. solution)	10 cc.

The two solutions are mixed **just before using** and the tissue, cut into pieces 1 cm. or less in thickness, and allowed to remain not over four days, with two changes. Thorough washing in running water for 18–24 hours is important, followed by 80 per cent. alcohol. This fluid yields excellent results, the cellular fixation being satisfactory and the required time not excessive. Small pieces of tissue, not exceeding .5 cm. in thickness may be fixed and hardened within a few hours if kept at a temperature of 45° C. in an oven.

Formalin Solution.

Formalin (40 p.c. formaldehyde solution)	10 cc.
Water	90 cc.

Objects remain for 48 hours, or longer, and are then transferred to 95 alcohol for at least two days. This 4 per cent. aqueous solution of formaldehyde has convenience as its chief recommendation, since, when used alone it is deficient as an accurate fixative and often does not favor staining. Where, however, the gross features of a specimen are to be supplemented by microscopic examination, formalin offers a satisfactory compromise for the anatomist, pathologist, and histologist. Another important use of this formalin solution should be remembered, namely, the preservation of embryos. The reagent is so readily obtained, that the gynecologist, upon whom the embryologist must depend for his supply of human material, can secure, with little trouble, valuable specimens which are too often lost.

Bouin's Fluid.

Picric acid, saturated aqueous solution	75 parts.
Formalin	25 parts.
Acetic acid (glacial)	5 parts.

One gram of picric acid crystals will saturate about 75 cc. of water. This is a good nuclear fixative. The fixative is removed from the tissues by

repeated changes of 70 per cent. alcohol. It may be hastened by the addition to the alcohol of a few drops of a saturated aqueous solution of lithium carbonate, and by keeping the fluid containing the tissue in a warm place.

Allen's Modification of Bouin's Fluid; (B. 15).

To the above mixture freshly made and raised to a temperature of 38° C., are added and thoroughly dissolved the following, in the order stated: 1.5 grams, chromic acid crystals, and then 2 grams of urea crystals. Each of these should be dissolved as added, or a precipitate will be formed when the urea is put in. This is excellent for fixation of chromosomes. (Ezra Allen, '18).

Flemming's Solution.

Osmic acid (2 p.c. aqueous solution)	4 parts.
Chromic acid (1 p.c. aqueous solution)	15 parts.
Glacial acetic acid	1 part.

The mixture is best prepared just before using, although it will keep for some time without serious deterioration, if tightly stoppered. Owing to the cost of the osmic acid, the solution should be used with economy. The tissue, in pieces not over a few millimeters in size, remains in the mixture for 1–2 days, or even longer, is then washed in running water for 12–24 hours and transferred, by ascending strengths, to 80 per cent. alcohol, in which it may be preserved. This reagent, although somewhat expensive is of great value in studies concerning cell-structure and mitosis. Its power of penetration, however, is very limited; it is necessary, therefore, to use pieces as small as possible, otherwise the desirable action of the osmic acid will be confined to the peripheral zone, whilst the deeper parts of the tissue will be influenced chiefly by the chromic acid alone.

EMBEDDING AND CUTTING SECTIONS

Having secured properly fixed and preserved tissues by one or more of the preceding methods, such tissues must be cut into thin sections, stained, rendered transparent and mounted before they can be satisfactorily examined under the microscope. Whether sectioning or staining takes precedence depends upon the character of the object and the end in view. If the object be an embryo or some structure for whose study it is desirable to secure a series of sections in strict sequence, or sections of the least possible thickness, the **paraffin method** is chosen. If, however, these particular features are unimportant and the production of thoroughly good preparations for general histological study is the result in mind, the **parlodion method** offers advantages and is usually selected. Further, if it is desired to cut serial sections of tissue requiring only a single staple stain, as carmine or hematoxylin, to demonstrate satisfactorily its general structure, much labor is saved and risk of losing sections avoided by staining the object **in toto** before sectioning in paraffin. Unless this is done, the supporting paraffin must be removed by a solvent (xylol) and the sections, previously fixed to the slide, stained in position, a procedure requiring considerable time and care when long series are to be treated. Since, except for embryos and special work, the retention of the sections in strict sequence is not usually necessary, staining in bulk is much less frequently followed than staining after cutting. When cut in parlodion the sections may be conveniently treated in large numbers at one time and contrast dyes employed with little additional trouble.

Whichever method be chosen, parlodion or paraffin, the fundamental principle is the same—the complete impregnation or saturation of the object with the embedding mass, so that when the tissue is cut into thin sections even the most delicate and isolated parts shall be retained in position by the support of the mass. This constitutes **interstitial embedding,** as distinguished from **superficial,** by which the object is merely surrounded with some material as tallow and wax, that affords superficial support, but does not bind together the structural components. In either case, whether parlodion or paraffin, the tissue must be carefully dehydrated before being placed in the fluid embedding material. Upon the proper carrying out of this step depends the success or failure of the embedding, since if water still remain within the object, the embedding substance fails to penetrate its deeper parts and the interstitial embedding is incomplete.

Dehydration must be thorough, for unless all the water be extracted from the object the subsequent penetration of the embedding substance will be imperfect and the sections uneven or torn. This essential step is effected by alcohol. Assuming that the tissue has been stored in 70 or 80 per cent. alcohol, the usual strength for this purpose, it is transferred to a tightly-stoppered wide-mouth bottle, of 200 cc. capacity, containing 95 per cent. alcohol, for 24 hours. It is then placed in a similar bottle, of 100 cc. capacity, containing absolute alcohol, for 24–48 hours, during which the absolute alcohol should be changed. The exact length of time needed for complete dehydration varies with the density and the size of the object, delicate small objects, such as small embryos, evidently requiring much less time than compact and large ones. It is always better to allow ample time for the extraction of the water, since undue haste in this particular may require tedious retracing of subsequent steps.

PARLODION EMBEDDING AND CUTTING

Assuming that the tissues have been fixed in Zenker's or Helly's fluid, and have been kept in 80 per cent. alcohol, the steps in the parlodion method are as follows:

1. 95 per cent alcohol..... 24 hours.
2. Absolute alcohol..... 24 hours.
3. Absolute alcohol, anhydrous copper sulphate..... 24 hours.
4. Absolute alcohol and ether, equal parts, anhydrous copper sulphate..... 24 hours.

It is essential to have solutions 3 and 4 dehydrated by the addition of anhydrous copper sulphate. Dessicators are very convenient for this purpose. The copper sulphate lies on the bottom and filter paper is interposed so as not to place the tissue directly on the copper sulphate. The copper sulphate keeps the alcohol and ether absolute and thus the tissues are dehydrated more thoroughly.

5. Parlodion I..... 24 hours.
6. Parlodion II..... 24 hours.
7. Parlodion III..... 24 hours.
8. Parlodion IV..... 24 hours.
9. Parlodion V..... 24 hours.

It is necessary to prepare parlodion with great care. The greatest importance lies in seeing that no water is present in it, for this will interfere with dehydration, embedding, and cutting. To prepare parlodion:—Wash the

shreds well in distilled water (3 times). Place them on a linen towel, or filter paper, to absorb the excess water. Place them in the oven at about 45° C. for 24 hours. When dried, place the shreds in an Erlenmeyer flask and pour over them equal parts of absolute alcohol and ether which have been treated with anhydrous copper sulphate. See that the bottle is well stoppered so that no moisture gets in. When making parlodion at first add equal parts of alcohol and ether, 200 cc. of each to 1 ounce of parlodion. Let it dissolve; this is aided by stirring occasionally. From this solution, make all necessary dilutions by the addition of the solvent solution of absolute alcohol and ether. Make IV from V by diluting with an equal quantity of the solvent solution. Proceed in the same way in making up III from IV, and proceed in a similar manner for the successively thinner dilutions. It is always well to have a very thick solution, slightly thicker than No. V parlodion, on hand for that is the stock which will be necessary to use for the final blocking.

Embedding and Evaporating.—Pour some of the thick parlodion from the stock bottle into a stender dish. (Have the solution twice as high as the height of the tissue to allow for evaporation.) Take the pieces from parlodion V, and place them in the parlodion in the stender dish, orienting them carefully in case one particular plane of section is needed. For the first day place the cover on the stender dish tightly to allow any bubbles of air to escape from the tissue and to come to the surface. If after 24 hours air is seen under the tissue, move it gently with needles and allow the air to escape. It is important to secure a uniform evaporation of the parlodion. This is effected in the following manner:—After the first day place the cover of the dish just off the ground area or put a string over the side of the dish and lay the cover on it. This will give sufficient opening to allow the alcohol and ether to escape. The total time for this evaporation-process should be from 5 to 7 days. In fact, the slower the evaporation, the better the results obtained for it is necessary to have an homogeneous consistency of the parlodion from top to bottom to ensure successful cutting. If, for instance, one notices that it evaporates too fast so as to cause the surface of the parlodion to be hard while the bottom is still soft, it is necessary then to put the cover on tightly. This will allow the alcohol and ether vapors to work through from the bottom and to dissolve the crust formed on the surface, thus producing an even density throughout. This gradual evaporation should go on until the parlodion becomes of the density of hard rubber. When this density is reached pour 80 per cent. alcohol over the surface.

Before cutting the blocks out of parlodion they should have remained under 80 per cent. alcohol for at least 24 hours. The tissue is then cut out of the stender dish, trimmed to a suitable size and is ready to be mounted on a holder.

Mounting the Parlodion Block.—Take the parlodion block and dip it successively into 95 per cent. alcohol, absolute alcohol, mixture of equal parts of absolute alcohol and ether, thick parlodion, and immediately place it on a holder preferably a fibre-block, being careful not to have bubbles between the parlodion block and the holder. This mount remains in the air about 1 to 2 minutes to allow the parlodion to form a crust. It is then placed in 65 per cent. alcohol for at least one half hour before cutting.

Cutting and Mounting Sections.—First remove the superfluous parlodion with a sharp razor leaving a narrow zone 1 to 2 mm. in width around the object. In cutting the sections several points must be observed.

The parlodion block must have been fastened firmly on the fibre-block so that no air is under it forming a cushion or the sections will not be uniform in thickness. The knife must not be set at too great an angle, but so that after the edge of the knife engages the block, it passes through the latter very obliquely and nearly the whole length of the blade is used in cutting the section.

The knife and the object, while it is being cut, is continuously moistened with 65 per cent. alcohol. If the sections are for class use or if no series is required, the sections are cut, and taken off by a spatula from one end of the knife, and then immediately transferred to 80 per cent. alcohol. They are then passed down through graded alcohols and are stained loosely.

Preparing Serial Parlodion Sections.—(Clove oil method). For staining sections on slide with parlodion removed.

a. The sections are cut at any thickness desired, and as each section is cut off it is carried over towards the heel of the knife. This is continued until a row of sections is cut. Great care must be taken that they do not dry, float around, or wash off when one applies more alcohol.

b. A clean slide is smeared with egg albumen mixture, which is made as follows:

50 parts of egg albumen (strained),
50 parts of glycerine, C. P.,
Crystal of camphor.

c. A spatula is brought forward against the heel of the knife and the sections are slid onto the spatula, keeping them in proper order. The excess of alcohol is drained off the spatula by placing its tip against a towel. This prevents the albumen from coagulating too soon. The sections are then placed on the slide in the same order in which they were cut.

d. When the slide is filled with the number of sections desired, they are pressed with a very fine filter paper. The filter paper is placed over the slide, pressed firmly and at the same time is rubbed in all directions. This removes all excess alcohol, and flattens the sections, making them adhere to the slide.

e. The paper is at once removed and immediately, without a second's delay, the clove oil is poured over the sections on the slide. Here they must remain in clove oil until the sections clear and become transparent in the oil. They may remain here for several hours or even days.

f. In preparing the sections for stain the procedure continues as follows: The clove oil is poured off the slide and then the slide is carried through the following solutions. Coplin jars are convenient.

95 per cent. alcohol + iodine, orange color (for tissues fixed in Zenker's)	5 to 10 minutes.
95 per cent. alcohol + iodine orange color	5 to 10 minutes.
95 per cent. alcohol clear. To wash off iodine	5 to 10 minutes.
95 per cent. alcohol clear. To wash off iodine	5 to 10 minutes.
95 per cent. alcohol + ether, equal parts. To remove excess parlodion	5 to 10 minutes.
95 per cent. alcohol	5 minutes.
80 per cent. alcohol	5 minutes.
60 per cent. alcohol	5 minutes.

Water if necessary.

They are then stained in the usual way.

Another Method of Fastening Parlodion Sections to Slide Without Clove Oil.—The sections having been well pressed with filter paper, the slides are at once placed in 95 per cent. alcohol. This method, however, does not work well for series, for by the time several rows of sections are placed on a slide, the egg albumen over all the slide has coagulated and as a result, the last sections placed on the slide are likely to come off.

To stain sections on slide, (without removing parlodion).

1. Press the sections on the slide with a fine filter paper.

2. Pour over the sections, at once, solution of equal parts of alcohol and ether.

3. Let stand until alcohol and ether evaporate and parlodion has become dry. This will fuse the sections and fasten them to the slide, but under no circumstances allow the tissues to dry.

4. Immediately press firmly with a fine filter paper.

5. Place at once into 95 per cent. alcohol, and allow to remain there for at least an hour.

The sections may be stained and treated in the usual way, but no aniline dyes can be used.

Paraffin Embedding.—The paraffin method requires some means of maintaining a constant temperature in order to keep the paraffin fluid, but only slightly above its melting point. This may be done with a water bath or by the heat from an electric bulb suspended over the dish of paraffin.

Paraffin should be of two kinds, one—the soft—with a melting point of 45° C., and the other—the hard—melting at 54° C. It is important that the paraffin be of good quality, that supplied by reliable firms being chosen. The quantity used is so inconsiderable that the slightly increased cost is of little consequence in comparison with the satisfaction of having a dependable article. Neither of the above grades is used alone, but a mixture of the two, so proportioned that the resulting mass has a melting point of about 52° C. The proportions vary so with the season and temperature of the laboratory that no exact figures can be given, but, in a general way, about equal parts will yield a satisfactory mass for ordinary use. When the object is relatively hard and very thin sections are desired, harder paraffin is employed than usual. A nice adjustment of the consistence of the embedding mass to the character of the tissue and the particular purpose in view is an important factor in securing satisfactory results.

The manipulations in paraffin embedding are as follows:

1. The thoroughly dehydrated tissue is transferred from absolute alcohol to:

2. Chloroform, 4–24 hours, depending upon the size of the object, small delicate embryos requiring often only 1–2 hours. When the alcohol is completely replaced, the tissue floats below the surface or sinks.

3. Saturated solution of paraffin, in chloroform, 6–24 hours, depending upon the size and density of the object.

4. Melted paraffin in a small open porcelain or glass round-bottom dish, 2–12 hours, in oven at 52°–54° C. The paraffin must be carefully guarded against overheating to prevent injury to the tissue. After 1–2 hours, the object should be transferred to a second dish with fresh melted paraffin. So long as chloroform is present, the embedding is incomplete. In order to test these conditions, a rod may be judiciously heated, and held for a few moments in the paraffin in the vicinity of the object, when, if still present, the chloroform is liberated as small bubbles. When the chloroform

has been driven off, the object is transferred once more to fresh paraffin preparatory to embedding. This last transference is delayed until there is reason to believe that the object is completely saturated with the embedding mass and free from chloroform, since the presence of the latter is unfavorable to the desired homogeneity of the embedding mass.

5. Embedding is accomplished by surrounding the object with melted paraffin in a folded paper box, or, still better, an adjustable metal frame. When an embedding frame is employed—and its convenience recommends it—it is adjusted to suitable size and placed upon a piece of glass resting on the flat bottom of a deep dish. The frame and sheet of glass should be warmed to prevent the too rapid solidifying of the paraffin. The object may be transferred to the embedding box by pouring when the box is filled, or by transferring with a warmed loop of platinum wire. Before the paraffin ceases to be fluid, the position of the object, with regard to the desired planes of sections, must be carefully adjusted by means of heated needles.

When the proper orientation of the object has been secured, cold water is poured into the dish, care being taken neither to shake the object, and thereby disturb its position, nor to allow the water to rise above the sides of the frame. The mass is allowed to remain for a few moments, until the surface of the paraffin is completely covered by a thin pellicle of congealed substance. When this has occurred, the water is very gently added and the entire frame and contents submerged. If the water be allowed to come into contact with the still fluid paraffin, cavities containing water may be imprisoned within the block—an accident that may interfere with proper cutting. In order to secure homogeneous paraffin, a most desirable feature for satisfactory sectioning, it is necessary to solidify the melted mass as rapidly as may be done with prudence. If it be allowed to cool slowly, crystallization occurs and the mass becomes opaque and friable. After thorough cooling and hardening, the frame is removed and the mass, if still adherent to the glass plate, carefully loosened. Tissues properly embedded in paraffin may be kept for years without deterioration, if guarded against dust and excessive temperatures. Indeed, delicate objects, as embryos, are much more satisfactorily preserved after being carefully embedded than if kept for a long period in alcohol. It is often convenient and economical to embed two or even more small objects at one time in the same block, care being taken to mark, by some ineffaceable label, the character and cutting planes of the enclosures.

Several methods of double embedding have been devised with a view of combining the advantages of parlodion with those of paraffin. For particular lines of work they are valuable and fairly satisfactory. Their description will be found in the special books on microscopical technic.

Paraffin sections are cut dry. When the object is large and not delicate, the paraffin block may be clamped directly in the jaws of the object holder. If, however, the object is of small size and great delicacy, as an embryo, the block of paraffin with the embedded tissue is fastened to one of the metal "tables" supplied with the microtome. This is best accomplished by covering the surface of the metal disk with a thin layer of melted paraffin on which the embedded object is firmly pressed, additional security being given by running a heated knife or other convenient tool around the base of the block. After thorough cooling, the block is ready for trimming preparatory to sectioning. This should be done with a sharp knife, care being

taken that in shaping the block the slices of paraffin are not too thick, lest the enclosed object be subjected to undue pressure. While all superfluous embedding mass should be cut away, the trimming must not be too close, a margin of paraffin, one or two millimeters broad, being left around the object.

For ordinary purposes, the knife scrupulously clean, is set at angle and carried obliquely through the tissue. For routine examinations, sections 7–10 μ thick, will be sufficiently thin, particularly when of some size. If, however, cell-structure and other details requiring the use of high amplification are in view, the sections can not be too thin. Under the most favorable conditions, it is possible to obtain sections of small size which are not over 1 μ in thickness.

If the consistence of the paraffin and tissue be just right and the sectioned surface not too large, the sections will lie flat and smooth on the knife, from which they are removed as cut and placed on a clean sheet of paper. Protected from dust and excessive temperature, they may be put aside for mounting at some future time. If, however, they are allowed to lie too long, particularly in a warm temperature, there is danger of their sticking to the paper; early mounting is, therefore, to be recommended. After the sections desired at that time have been cut, the block may be put aside for subsequent use. If the paraffin is hard the sections will roll up on the knife. This annoying feature may be prevented by lightly holding down the edge of the section with a small sable brush in the left hand as the knife is drawn through the tissue. In this manner flat sections may often be secured when, without manipulation, they would be tightly and hopelessly rolled.

When the paraffin is too hard, still contains chloroform, or lacks homogeneity, it often is brittle and crumbling, so that the sections break before completed. Too little consistence of the embedding mass is also unfavorable for satisfactory cutting, since, if the paraffin is too soft, insufficient support is given the sections, which then come off more or less wrinkled and compressed with corresponding distortion of the object. If the compression is not excessive, the sections may be often restored to their normal form by floating them on judiciously warmed water, where they expand. Obviously care must be taken that the temperature of the fluid is not sufficiently high to dissolve the supporting paraffin. The temporary reduction of the temperature of the room, by opening an adjacent window, frequently serves to correct undue softness of the embedding mass. Similarly, bringing a gas-flame, or other source of heat, into the vicinity of the microtome sometimes enables satisfactory sections to be made with over-hard paraffin. Care must be observed to keep, by an occasional touch with a dry cloth, the knife clean and free from adherent particles of paraffin, especially the under surface of the cutting edge. If this precaution be neglected, an attached fragment of paraffin may ruin important sections by causing fissures and breaks. A properly ground and really sharp knife is an indispensable requisite for the production of successful preparations.

Serial sections are most easily cut in the form of "ribbons." While of course, their sequence may be preserved by carefully arranging isolated sections in the order in which they are cut, much time and trouble are saved by adopting the ribbon-method whereby the sections are caused to adhere and form a long chain. The method is particularly suitable for small and delicate objects stained **in toto**, as embryos, which are to be entirely cut into sections. The knife is set at right angle to the microtome track and the

paraffin block so trimmed (the desired plane of section being first secured by the microtome adjustments) that the two long sides of the rectangular block are exactly parallel, not only with each other but also with the edge of the knife. Since the mounted sections will be separated by twice the width of the border of paraffin surrounding the object, the block should be trimmed as close as possible to the tissue, a thin covering of paraffin, however, being left over the upper surface of the object.

Everything being in readiness, the object is raised to a height sufficient to allow several sections of the overlying paraffin being made without involving the object. After cutting a few sections that include the entire surface of the block, the knife is returned to the beginning of the track, the block elevated by the micrometer screw, and, without removing the section, the blade drawn across the block for the next section. If the consistence of the paraffin is proper, the last cut section pushes the preceding one before it on the blade and, at the same time, adheres to it. The manipulation is repeated and, if all goes well, each succeeding section adheres to its predecessor and advances the chain. For embryological work, in which ribbon cutting is particularly useful, the sections should be of uniform thickness, 10 μ being satisfactory for most purposes. Sections less than 5 μ in thickness seldom yield good ribbons. The same is true of very thick ones. A small sable brush held in the left hand is useful in keeping the first few sections flat, in brushing away shreds of paraffin, and in supporting the ribbon after it has become too long to lie on the knife. Under favorable conditions and with careful support, ribbons one or two feet in length, or indeed much longer, may be cut readily. With the ordinary sliding microtome, it is safer to remove the chains to an adjacent sheet of clean paper when they reach a length of ten or twelve inches, care being taken that the last cut two or three sections remain undisturbed on the knife to guide the succeeding ones. The under surface and edge of the knife must be kept free from particles of paraffin, otherwise breaks and fissures in the sections may occur.

As the cutting proceeds, it may become necessary to retrim the block since, unless the sides have been cut strictly vertical and not, as they often are, slightly sloping, the border of paraffin becomes gradually excessive. Then too, the front and back edges of the block must be parallel, otherwise the ribbon will curve instead of remaining straight. After the cutting is well under way, any considerable change in the plane of section should be avoided if it is important to secure a complete series, as such change usually necessitates the loss of several sections. If the embedding mass be too hard the sections will not adhere and, of course, the ribbon not form; if too soft the sections will wrinkle and compress and, perhaps, not advance. These defects may often be overcome by appropriate changes in the temperature of the room, or by judicious local application of cold or heat to the block itself. When other means fail, coating the block with paraffin of appropriate consistence often affords relief. Now and then, especially when using rather hard paraffin on a cold, bright, dry day, the atmospheric conditions are such that sufficient electricity is liberated during sectioning to disturb seriously the sections. The latter may break apart and shorter or longer pieces of the ribbon attach themselves to one another or to the microtome or knife. A repetition of this exasperating accident may usually be avoided by charging the atmosphere with moisture, often conveniently accomplished by liberating steam.

STAINING

The object of staining is to bring out the various structural components of the tissues by taking advantage of their selective affinities for certain dyes. The differentiation usually sought has as its first object,the display of the nucleus; next, the tingeing of the cytoplasm; and thirdly, the exhibition of the intercellular substances. Of the large number of staining methods which from time to time have been devised to meet the requirements of particular lines of work, only a few of the most reliable and generally useful will be here given. For the ordinary needs of the histologist staining with hematoxylin, followed by eosin, leaves little to be desired, since, when successful, the nuclear differentiation is sharp while the cytoplasm and intercellular substances are sufficiently tinged to produce clear and instructive pictures. When, as in the case of embryos, it is convenient to stain in bulk before sectioning in paraffin, borax-carmine will be found a most reliable dye, possessing penetration and uniformity of action in a highly satisfactory degree.

Ehrlich's Hematoxylin.

Hematoxylin crystals	2 gm.
Absolute alcohol	100 cc.
Distilled water	100 cc.
Ammonium alum	in excess
Glycerine	100 cc.
Glacial acetic acid	10 cc.

A. Dissolve the hematoxylin in the absolute alcohol and let stand in loosely corked bottle for a week, where the sunlight may reach it.

B. To the distilled water add ammonium alum in excess. Add A to B, while stirring vigorously. After several days add the glycerine and the glacial acetic acid and place the stain, in a corked bottle, in some suitable position insuring exposure to direct sunlight. Direct sunlight is important. During the next two weeks uncork for several days at a time. After three months the stain has "ripened" sufficiently for use. If kept in a well-stoppered bottle, with an excess of alum, the reagent retains its staining powers for years and, indeed, improves with age. Although requiring a long time until ready for use, Ehrlich's hematoxylin is most satisfactory, staining well with all the usual methods of fixation and, with proper precautions being permanent.

This, as all other hematoxylin stains, should be filtered immediatly before using. Depending upon the age of the solution and, to some extent upon the method of fixation, sections require to be left in the stain from 5 to 10 minutes. They are then washed thoroughly in running water for one or two hours. If deeply colored they may be placed in a dish of 70 alcohol, acidulated by the addition of 5 drops of hydrochloric acid to each 100 cc. of alcohol. The sections remain in the acid bath, in which they turn reddish, so long as they discharge color, keeping them moving and not allowing them to adhere. During subsequent washing, the blue color is restored, becoming brighter as the washing progresses. While the acid alcohol may be omitted with sections not too deeply tinted, full staining followed by the acid alcohol yields sharp nuclear differentiation and brilliant pictures. The employment of the acid bath may be recommended, therefore, as a routine procedure. Since the permanency of all hematoxylin preparations depends

upon the elimination of every trace of acid, prolonged and thorough washing is essential, otherwise fading will occur. If after short washing the sections are placed for a few minutes in water, to which a few drops of ammonia have been added, and then washed thoroughly in, preferably running, water, permanency of the staining is assured.

Böhmer's Hematoxylin.

Hematoxylin crystals	1 gm.
Absolute alcohol	10 cc.
Ammonium alum	10 gm.
Distilled water	200 cc.

Dissolve the hematoxylin in the absolute alcohol and keep in stoppered bottle for 24 hours. Dissolve the alum in the warm distilled water. When cool, gradually add the dissolved hematoxylin while stirring. Place in a open wide-mouth bottle or dish, protected from dust, for one week, when, after filtering, the stain is ready for use. Keep in a tightly corked bottle and filter the required quantity on using. Immersion from 10 to 30 minutes usually suffices to stain to the required degree. This solution stains well although not uniformly so intensely as Ehrlich's, and, if the sections are thoroughly washed, yields permanent results.

Delafield's Hematoxylin.

Hematoxylin crystals	4 gm.
Absolute alcohol	25 cc.
Ammonium alum	52 gm.
Distilled water	400 cc.
Glycerine	100 cc.
Methyl alcohol	100 cc.

The hematoxylin is dissolved in the absolute alcohol and the alum in the heated distilled water. After the alum solution has cooled, the hematoxylin is slowly added while stirring and the fluid allowed to stand in a wide open vessel, as a beaker or jar, protected from dust but exposed to light and air, for about 15 days. Filter and add glycerine and methyl alcohol. Expose to the light until the stain acquires a dark purplish tint, then filter and keep tightly stoppered. The advantages of Delafield's hematoxylin are less for coloring sections than for staining tissue in bulk. For mass-staining the freshly filtered solution is diluted with five to ten volumes of distilled water, in which the pieces of tissue remain from 24 to 48 hours, or longer, until uniformly darkly tinted throughout. The stained tissue is rinsed in distilled water and placed in acid 70 per cent. alcohol (5 drops hydrochloric acid in 100 cc. alcohol) from 4 to 8 hours. After this differentiation the tissue must be thoroughly washed in running water for 12 to 24 hours to remove every trace of acid and to bring out the rich blue color.

Contrast staining after hematoxylin, especially when the latter has been limited chiefly to the nuclei, adds much to the effectiveness of the preparation. Such double staining may be accomplished by treating the hematoxylin sections with solutions of acid fuchsin, Congo red, or eosin. The latter answers well and is convenient. The most satisfactory results are obtained with "water soluble" eosin (not "alcohol soluble"), of which a .5 per cent. solution in 70 per cent. alcohol is preferable, the sections remaining until decidedly rosy, usually a matter of 1–2 minutes. They are then transferred to 70 per cent. alcohol, in which they remain so long as

clouds of eosin are discharged; after one or two changes of 70 per cent. alcohol and no further color is given off, the sections are passed as rapidly as thorough dehydration will permit through 95 per cent. alcohol, then cleared in carbol-xylol, and mounted in balsam as will be presently described.

Grenacher's Borax-Carmine.

Carmine (No. 40)	3 gm.
Borax	4 gm.
Distilled water	100 cc.
70 per cent. alcohol	100 cc.

The carmine and borax are rubbed together in a mortar in the warmed distilled water until dissolved. After cooling, the alcohol is added and the unfiltered solution placed in a stoppered bottle. The stain is not ready for use until it has stood for several weeks. The quantity required for staining which may be repeatedly employed should be decanted and filtered before using. Although sections may be stained with the solution, its chief value is for mass-staining, since its powers of penetration and uniform coloration are excellent. Assuming that the solution is to be put to this use, the object is transferred from 70 per cent. alcohol to the undiluted stain, in which it remains 24–48 hours and is then directly placed, that is without washing, into acid alcohol (8 drops of hydrochloric acid to 100 cc. of 70 per cent. alcohol) for 8–24 hours, or longer, depending upon the size and density of the object. The purpose of the acid bath is to differentiate the nuclei and fix the stain. Deep staining and thorough differentiation produce the most satisfactory preparations. After two changes of 70 per cent. alcohol, the object remaining from 2–3 hours in each, it is dehydrated in 95 per cent. and absolute alcohol preparatory to embedding.

Contrast staining after carmine may be carried out with .5–1 per cent. alcoholic solutions of such aniline dyes as methylene blue, methyl violet, or methyl green. The labor and time involved in staining serial sections on the slide, as of course must be done, as well as the limited endurance of the aniline tint, ordinarily deter from double staining. Although the second dye yields pleasing preparations, unless there is some special reason to warrant the additional labor, the contrast color may be omitted with serial sections of tissues stained in bulk.

Staining sections on the slide is necessary when it is desirable to tinge uncolored paraffin sections or to add a contrast tint to those stained in bulk before cutting. Since the paraffin must be removed from the section before the stain can act, it is evident that the support afforded by the embedding mass must be replaced by that of the slide before the paraffin may be removed with safety. The sections must, therefore, be fixed to the slide, so that subsequent manipulations will not disturb even the most delicate and isolated parts of the sectioned object.

All slides and cover-glasses used for mounting preparations must be thoroughly cleaned. This is readily accomplished by soaking the slides and cover-glasses in strong sulphuric acid for 5–10 minutes, care being taken to immerse the pieces separately and not to allow them to adhere. They are transferred, piece by piece, to a large vessel, containing water and washed thoroughly under the tap, with occasional separation and agitation until all traces of the acid are removed. The slides and covers are then placed in 95 alcohol and carefully dried by wiping with a clean linen cloth of appropriate

thickness, from which all sizing and starch have been removed by previous laundering. Neglect to provide properly cleaned slides and covers mars many valuable preparations.

The method of **fixing to the slide** should be made, if possible, to serve an additional and important purpose, namely, to expand and to flatten out the paraffin sections, which very often are slightly compressed and wrinkled. To mount them in this condition may seriously interfere with their later use, as in the case of serial sections of embryos in making reconstructions. When the fixed sections are not to be treated with watery solutions, a convenient and satisfactory means is the **gum method,** carried out as follows: Of a saturated aqueous solution of best gum arabic (a crystal of thymol being added to prevent the growth of fungi) about 12 drops are added to 30 cc. of distilled water and thoroughly shaken. The clean slide is flooded with the solution, care being taken that the solution does not run over the edges and the sections are floated on the liquid, all parts of the sections being separated from the slide by a stratum of the solution. When all the sections are arranged the slide is placed on a warm metal plate and very cautiously heated, the temperature never being allowed to rise to the melting point of the paraffin, the object being to secure the expansion of the sections while swimming on the gum solution. They expand in a few minutes. The excess of fluid is then drained off, the sections are finally rearranged with a needle and the slide, protected from dust, is set aside to dry. The latter must be thorough, and requires, therefore, some hours, a good plan being to leave the sections undisturbed over night.

The **albumen-glycerine mixture** is another excellent fixative, which has the advantage over the gum solution of being unaffected by water. This consists of equal parts of the strained white of a fresh egg and glycerine thoroughly stirred with a glass rod. A small drop of the fixative is placed on the slide and spread out as evenly and thinly as possible. A number of slides may be prepared, dried, and suitably stored for subsequent use. The albumen-coated slide is now covered with a thin stratum of water, the sections arranged, and the slide then placed on the top of the oven, or other appropriate warm location, where the sections expand and the water evaporates.

Removing the paraffin is the next step preparatory to staining sections on the slide, whatever method may have been employed to secure their attachment. To accomplish this the slides with the securely affixed sections are immersed for a few minutes in xylol, which promptly dissolves the paraffin and leaves the cleared sections in place, freed from the embedding material. The slides are then transferred to 95 per cent. alcohol to displace the xylol, after a few minutes passed to fresh alcohol, and then carried through 70 per cent. alcohol into the staining fluid, if that be an alcoholic solution, or into water, in case the stain be chiefly aqueous. The most convenient receptacles for exposing a number of section-loaded slides to the various solutions are the square glass "staining-jars", provided with grooves and covers, which allow several pairs of slides, placed back to back, to be stood on end and immersed at one time. The disadvantages of the square jars in common use are the danger of damaging the sections by contact with the grooves and the lack of a ground-joint to prevent evaporation, as when containing xylol or absolute alcohol. Although less readily procured, Coplin jars, with ground covers, meet every requirement. When of the proper height and diameter, they permit five pairs of slides to be

immersed at one time with convenience and safety and enable volatile fluids to be used repeatedly without deterioration. After the staining has been completed according to the details of the method selected, the sections are passed through jars containing 95 per cent. and absolute alcohol to insure complete dehydration prior to clearing and mounting.

Clearing the sections is necessary to render the otherwise more or less opaque tissue transparent and suitable for microscopical examination. If the tissue contains no trace of water, it may be mounted in pure Canada balsam, the usual medium in which objects are preserved as permanent preparations, directly from xylol, the latter being replaced by the highly refracting balsam and the required transparency thereby secured.

The means employed to secure this transparency depends upon the condition of the tissue, whether infiltrated with the embedding mass, as in the case of parlodion sections, or free from such support, as in the case of paraffin sections attached to the slide.

Parlodion sections are best cleared in a **carbol-xylol mixture,** consisting of one part of pure carbolic acid to three parts of xylol. The dehydrated sections are transferred to this fluid from the strong alcohol and after a few minutes become transparent. If, however, the required transparency fails to appear after five or ten minutes, it may be concluded that the dehydration has been insufficient to allow the penetration of the clearing solution. The sections must be returned, therefore, to the alcohol. In all cases thorough dehydration must be insured by adequate treatment with strong alcohol.

Paraffin sections, after the removal of the paraffin by immersion in xylol, are transferred to some clearing fluid, oil of turpentine answering well and being inexpensive.

MOUNTING AND FINISHING

Unless required for only cursory examination, the sections are mounted in some medium suitable for further study and preservation. The most satisfactory medium for general use is pure Canada balsam, which is supplied in convenient collapsible metal tubes, from which the required amount may be pressed. In the case of tissues cut in parlodion, the individual sections are transferred from the dish of clearing solution (carbol-xylol) to a clean slide by means of a thin metal section-lifter, a clean mounted needle being used in guiding and holding the section on the lifter, as well as in transferring it to the slide from the lifter. When the latter is broad, the blade should be perforated to facilitate raising the section from the fluid, as well as draining off the clearing solution. After being placed on the slide, the superfluous carbol-xylol should be carefully removed by filter paper, and the section finally arranged by judicious use of the needle and a drop of balsam gently pressed out from the tube upon the middle of the preparation.

If the balsam has the proper consistence, about that of syrup, the slide is held for a few moments over an alcohol flame, the slight heating facilitating the distribution of the balsam over the section. The cover-glass, previously

scrupulously cleaned and in readiness, is grasped between the clean blades of the forceps, held for a moment over the alcohol flame, and gently lowered on the slide in such manner that the left edge of the cover is brought first into contact with the balsam. As soon as this contact is made, a moment's pause is advantageous to allow the balsam to spread out beneath the cover, which is then steadily and slowly lowered into position over the specimen until the entire space between the slide and cover is filled with the mounting medium. If, after very gentle pressure on the cover-glass with a clean needle, part of this space remains unfilled, additional balsam must be run in until the space is completely occupied by the mounting medium. Care must be exercised lest any excess of balsam get on the surface of the cover; otherwise it does not interfere with the immediate examination of the preparation. A slight edging of balsam around the cover is useful, since it dries much sooner than the medium beneath the cover and thereby adds materially to the fixation of the latter. While avoiding as far as possible the imprisonment of air-bubbles, should these be present after the cover is in place, they need cause no concern, as they usually spontaneously disappear during the next twelve hours, unless enclosed within some recess or fold in the section.

While the preparation may be examined under the microscope as soon as properly mounted, care being taken to keep it horizontal to avoid possible slipping of the cover-glass, no attempt should be made to finish it until the balsam around the edges of the cover has sufficiently hardened to preclude displacement. Ordinarily this requires some weeks, but the process of hardening may be facilitated greatly by subjecting the freshly mounted specimen in some suitable place protected from dust, to continuous gentle heat. After a few days of such drying, although the balsam in the centre of the preparation may remain fluid, the cover will be so securely fixed that the specimen may be finished and labelled. If the superfluous balsam be considerable, as much as possible should be removed by the knife, care being taken not to touch the cover-glass, and the slide finally cleaned with a cloth moistened with xylol. Disturbing the cover-glass will likely ruin the preparation and, hence, this danger is to be constantly borne in mind.

After the slide has been cleaned, not forgetting the under side, labels are attached at the ends. Data of importance, regarding tissue, source, method of fixation, staining, and date, should be noted on a label and never be entrusted to memory; failure to observe such precautions is often a constant source of uncertainty and regret in later years. When preparations include serial sections, numbers or letters on the labels should indicate the sequence of the slides. Much time may be saved by marking the slides as to order with a writing diamond before they receive the sections. The second label is convenient for memoranda concerning special features shown by the preparation. Where many specimens accumulate, some system of card-catalogue well repays in convenience for future reference. The various methods of storing microscopical preparations are matters of individual preference and expediency, provided two essentials are observed—that the slides lie horizontal and are protected from light. With proper precautions against the presence of acid in the sections, even hematoxylin preparations may be preserved for many years without deterioration.

SYNOPSIS OF STANDARD METHODS

Assuming that the tissue is of moderate density, has been fixed in Zenker's fluid and preserved in 70 alcohol, with due precautions for the removal of the deposits of mercury, and that the size of the piece to be cut is approximately a surface of 1 sq. cm. by .5 cm. thick, the steps in the two standard methods—in the parlodion and the paraffin—are as follows:

Parlodion

1. 95 alcohol, 24 hours.
2. Absolute alcohol, 24 hours.
3. Absolute alcohol, copper sulphate 24 hours.
4. Absolute alcohol, ether, copper sulphate, 24 hours.
5. Parlodion I. 24 hours
6. Parlodion II. 24 hours
7. Parlodion III. 24 hours
8. Parlodion IV. 24 hours
9. Parlodion V. 24 hours
10. Evaporation, 4–6 days.
11. Mount on fibre-block.
12. Harden in 65 per cent. alcohol, 1 hour or longer.
13. Cut sections, wet with 65 per cent. alcohol.
14. Stain in Ehrlich's hematoxylin, 5–10 minutes.
15. Wash in water, 5–10 minutes.
16. Acidulated 70 alcohol, about one-half minute.
17. Wash in water.
18. Ammoniated water, until again blue.
19. Wash thoroughly in water.
20. Stain in eosin, 1–2 minutes.
21. 70 alcohol.
22. 95 alcohol, 5 minutes.
23. Clear in carbol-xylol.
24. Mount in balsam.

Paraffin

1. 95 alcohol, 24 hours.
2. Absolute alcohol, 24 hours.
3. Chloroform, 2–6 hours.
4. Saturated solution of paraffin in chloroform, 6–24 hours.
5. Melted paraffin in oven at 56° C., 1-3 hours.
6. Block in paraffin not previously used.
7. Cut sections, dry.
8. Expand sections on slide.
9. Dry slides to attach sections, 12 hours.
10. Xylol to remove paraffin, 3 minutes.
11. Absolute alcohol, 1–3 minutes.
12. 95 alcohol, 1–3 minutes.
13. 80 alcohol, 1 minute.
14. Water, 1 minute.
15. Hematoxylin, 5–10 minutes.
16. Water, 1 minute.
17. Acidulated water, 30 seconds. (Water with 0.5 per cent. HCl), decolorizes.
18. Water, 1 minute.
19. Ammoniated water, 1–3 min. (water with a few drops of ammonia. If too much ammonia, sections will come off), blue returns.
20. Water, 1 minute.
21. 50 alcohol, 1 minute.
22. 80 alcohol, 1 minute.
23. 95 alcohol, 1 minute.
24. Eosin in 95 alcohol, 40–60 seconds.
25. 95 alcohol 1 minute.
26. Carbol-xylol, 1 minute (to clear).
27. Xylol, 2 minutes.
28. Drop of balsam immediately. Cover with cover slip.

SOME USEFUL SPECIAL METHODS

Weigert's Myelin-Sheath Stain.—This method is used on sections of the central nervous system to demonstrate the fibre-tracts, and to show the arrangement of the gray and white matter. Proper fixation and mordanting are necessary for the success of the staining. The nervous tissue, either in the form of the entire brain or cord or of small portions of them, is fixed in 10 per cent. formalin. The duration of fixation for small pieces is one week or more; for the entire brain one to two months. If the tissues are to be set aside for further preparation at a later time, it is best to keep them in neutral 10 per cent. formalin.

After fixation the Weigert method requires the employment of four solutions, the primary mordant (A), the secondary mordant (B), the stain (C), and the differentiating fluid (D) made respectively as follows:

A. Primary mordant

Potassium bichromate	5 gm.
Fluorchrom	2 gm.
Distilled water	100 cc.

B. Secondary mordant

Copper acetate	5 gm.
Acetic acid, 30 per cent. or 36 per cent.	5 gm.
Fluorchrom	2.5 gm.
Distilled water	100 cc.

In making this solution, boil the fluorchrom and water in a covered vessel; turn off the gas, add the acetic acid, then the copper acetate: stir briskly until the latter is dissolved and allow to cool. The solution remains clear.

C. Hematoxylin stain

10 per cent. solution of hematoxylin in absolute alcohol.	10 cc.
Lithium carbonate, saturated aqueous solution	1 cc.
Water	90 cc.

It is very important that the hematoxylin be well ripened (two months or more), but the staining fluid should be made up just before using.

D. Differentiating fluid

Potassium ferricyanide	2.5 gm.
Sodium biborate	2.0 gm.
Distilled water	100 cc.

After fixation the blocks of tissue are washed in water overnight, before being placed in the primary mordant. Here they remain one week or longer, depending upon their size. After washing, they are passed into the secondary mordant for one to several days. The blocks are then washed in water, dehydrated in graded alcohols, and imbedded in parlodion. Sections are usually cut at 25–50μ. They are then placed in the staining solution overnight (20–24 hours) where they become a dense blue-black color. After staining the sections are washed thoroughly in water, best overnight. They are then placed in the differentiating fluid, and the decolorizing process watched. The color gradually leaves the gray matter, but is retained in the white matter, so that the contrast between the gray and the white matter becomes more and more distinct. The time for this process is usually between 20 minutes and an hour. The decolorizing is stopped by transferring the sections to water.

After differentiation the sections are to be thoroughly washed in water (overnight), dehydrated in alcohol, cleared in carbol-xylol and xylol, and mounted in xylol-balsam.

A variation of this method is to use the secondary mordant on sections instead of on the block. The procedure would then be,—fixation, primary mordant, embedding and cutting, secondary mordant (overnight), staining and differentiating.

Pal's Modification of Weigert's Method.—Fixation is in 10 per cent. formalin, one week or longer. This is followed by immersion in 2.5 per cent. potassium bichromate solution for 1–4 weeks. The tissues are then washed well in running water, dehydrated in graded alcohols, embedded in parlodion and cut at 25–75 μ. The sections are placed for 1–2 hours in a solution of 0.5 per cent. chromic acid to which has been added 1 cc. of 1 per cent. solution of osmic acid. Rinse sections in water, and stain 12–24 hours in the following hematoxylin stain, freshly made up.

Ripened 10 per cent. solution of hematoxylin in absolute alcohol	10 cc.
Acetic acid, 36 per cent	1 cc.
Tap water	100 cc.

Wash in tap water, 1–2 hours.

Immerse in a solution of a 0.5 per cent. potassium permanganate in water for 30 seconds, wash in water and finally place in the following solution:

1 per cent. potassium sulphite, in distilled water	100 cc.
1 per cent. oxalic acid, in distilled water	100 cc.

Mix the two solutions just prior to use. The differentiation must be watched as it may proceed very rapidly. If the differentiation is incomplete, the sections are again placed in the potassium permanganate solution, washed, and the process of differentiation repeated.

The sections are then transferred to distilled water, to which has been added a little lithium carbonate (water, 500 cc.; sat. aq. lith. carb., 1 cc.).

Wash well in water, 12–24 hours, dehydrate in graded alcohols, clear in carbol-xylol followed by xylol, and mount in balsam.

Wright's Blood Stain.

0.5 gm. of Wright's dry blood stain is dissolved in 100 cc. of absolute methyl alcohol. Complete dissolving of the powder may take 24 hours.

To Stain Blood Film with Wright's Stain.—Cover film on a coverglass with stain, wait one minute add distilled water, 6–8 drops, being careful not to let liquid run off cover slip. Stain 2–3 minutes; wash in water; drain off surplus water. Let dry thoroughly. When dry mount in balsam or damar.

Toison's Blood-Diluting Fluid.

Sodium sulphate	8.0	gm.
Sodium chloride	1.0	gm.
Neutral glycerine	30.0	cc.
Methyl violet, 5B	0.025	gm.
Distilled water	160.0	cc.

This fluid is used in diluting blood for total counts of red cells.

Ellerman's Method for Demonstration of Neutrophilic Granules in Tissue-Sections, as Adapted by Dr. M. N. Richter.

1. Fix small pieces of bone-marrow (2 mm. or less) in Helly's fluid for 24 hours.
2. Running water 24 hours.
3. Graded alcohols with iodine.
4. Embed in parlodion: cut sections thin, 7 μ.
5. Affix to the slide with albumen-glycerine.

6. Cover with clove oil until sections clear.
7. In alcohol and iodine to remove oil and traces of mercury.
8. Wash well in distilled water.
9. Formol-eosin mixture,–15 minutes.

1 per cent. bluish eosin, Grübler	5.0 cc.
Neutral formalin, 40 per cent	0.25 cc.

10. Distilled water at 45° C., 2–4 minutes.
11. Jenner's stain with equal quantity of distilled water–20–30 minutes.
12. Distilled water, 5 minutes.
13. Differentiate with absolute alcohol.
14. Xylol, to damar or neutral Canada Balsam.

All glassware must be as free from acid and alkali as possible. Preparations retain the stain a number of months. If mounted in green euparol they may keep a year or more.

Staining Blood Films by Jenner's and Giemsa's Stains.

Jenner's stain 3 minutes.
Add distilled water with pipette and allow to stand 2 minutes.
Pour off this (do not wash off).
Add Giemsa's stain diluted, and allow to stand for 10 to 15 minutes.
Wash off in distilled water, using dish of water.
Blot dry, with smooth blotter.
It is then ready to mount in balsam.

To make up Jenner's stain, for staining.

Jenner's stain	1 gm. Dissolved in
Absolute methyl alcohol	200 cc.

This keeps indefinitely.

To make up Giemsa's stain, for staining.

Giemsa's solution	10 drops
Distilled water	10 cc.

This should be used the same day.

Azur II and Eosin.

Stock solutions:

A. Azur II, Grübler	1:1000 in distilled water.
B. Eosin, wasserl. gelb	1:1000 in distilled water.

To stain:
Remove all parlodion from slide.
Wash sections thoroughly in distilled water.
Place in following for 12 to 24 hours:

Solution A	10 cc.
Solution B	10 cc.
Distilled water	80 cc.

Differentiate in 95 per cent. alcohol, absolute alcohol, and xylol. This stain is most successful on formol-Zenker material. Great care must be taken so that no alcohol gets into the dye, or it will precipitate at once. This stain is very valuable in the preparation of bone-marrow and for developing blood-cells in general.

Dominici's Stain.

Stock Solutions:

A.	Eosin, wasserl. gelb	0.25 gm.
	Orange G	0.3 gm.
	Distilled water	50.0 cc.
B.	Toluidine blue	0.25 gm.
	Distilled water	50.0 cc.

To stain.

Remove all parlodion, wash well in water.

1. Stain in solution A ..... 20 to 30 minutes.
2. Wash in 65 per cent. alcohol.
3. Stain in Solution B ..... 1 to 2 minutes.
4. 95 per cent. alcohol, absolute alcohol, xylol, mount.

This gives good results with material fixed in formol-Zenker or 10 per cent. formalin.

Fat Fixation and Staining.

1. Fix thin pieces (1–2 mm.) of fresh tissues 24–48 hours at 45–50° C. in the following solution:

10 per cent. aq. potassium bichromate	100 cc.
Glacial acetic acid	5 cc.

2. Wash in running water 12–24 hours.

3. Dehydrate and embed in paraffin in usual way, cut sections 3–5 μ and fasten to slide with albumen or water.

4. Remove paraffin with xylol; absolute alcohol.

5. Transfer directly to freshly prepared solution of Sudan III in 80 per cent. alcohol. 10 minutes are usually sufficient. Have Sudan III strong: boil alcohol solution a few minutes with large excess of dye: cool at room temperature and filter. Use within a few hours.

6. Rinse off excess stain in 70 per cent. alcohol, transfer immediately to water to stop action of alcohol.

7. (May precede 5). Stain a few minutes in Delafield's hematoxylin; wash in water.

8. Differentiate a few seconds in acid alcohol and transfer immediately to running water.

9. Mount in glycerine gum arabic.

Gum arabic,	5 gm.
Distilled water	5 cc.
Let stand 12 hours then add	
5 per cent. carbolic acid	10 cc.

E. T. Bell: On the differential staining of fats. *J. Path. and Bact.*, 19: 105—113. 1914.

Mallory's Aniline Blue Stain for White Fibrous Connective Tissue.

1. Fix in Zenker's fluid.

2. Embed in parlodion or paraffin.

3. Stain sections in a 0.5 per cent. aqueous solution of acid fuchsin for five minutes or longer, depending on the freshness of the tissue.

4. Transfer directly to the following solution and stain from ten to twenty minutes or longer.

Aniline blue, water soluble	0.5	gm.
Orange G	2.0	gm.
1 per cent. aq. solution of phosphomolybdic acid	100.00	cc.

5. Wash and dehydrate in several changes of 95 per cent., then absolute alcohol.

6. Clear in xylol.

7. Balsam.

For parlodion sections use clove oil method for removal of parlodion.

The white fibrous connective tissue stains blue: nuclei, red; erythrocytes, yellow; elastic fibres, pale pink or yellow.

Chrome-Silver Impregnation.—The introduction by Golgi of methods of silver impregnation has added an important means of demonstrating the astonishing richness and extent of the ramifications of the neurones and of the neuroglia cells. Of the several procedures suggested by Golgi the so-called **rapid method** is here given. It is most successful when applied to the nervous tissues of the fetal or new-born animals, and, at best, is capricious and uncertain.

The fresh young tissue is fixed either in **bichromate-formalin** (4 parts of 3.5 p.c. aqueous solution of potassium bichromate to 1 of 40 p. c. formalin), or in **Golgi's fluid,** (9 parts of 3.5 p. c. aqueous solution of potassium bichromate to 1 part of 2 p. c. aqueous solution of osmic acid).

Depending upon the object in view and the age of the animal, the tissue remains in the fixing fluid from 2–15 days. If fetal or very young, 2–3 days suffice for the neuroglia cells, 3–5 days for the nerve-cells, and 5–7 days for the collaterals. Older tissues require longer immersion, adult brain being left in the fluid from 8–15 days. After rinsing for a few moments with distilled water and quickly drying off with filter paper, the pieces, not over .5 cm. thick, are placed in 1 p. c. aqueous solution of silver nitrate. In this they remain 2–3 days or longer, during which a dark precipitate appears. In order to determine the probable success of the impregnation, free-hand sections are cut and examined in 95 per cent. alcohol under the microscope. If satisfactory, the desired nervous elements appear as sharply defined dark figures on a light, almost colorless background. Even in otherwise successful preparations, many parts of the section may be almost useless owing to deposits of silver-precipitate. The tissue is then dehydrated in absolute alcohol, embedded in parlodion as rapidly as possible and cut in 95 per cent. alcohol into sections not too thin. The sections are passed to absolute alcohol for thorough dehydration, then to creosote for 10 minutes, and, after remaining 5 minutes longer in xylol, finally placed on the slide, dried rapidly with filter paper, and covered with a large amount of balsam. The slide is now heated carefully over a flame until the balsam will set as soon as cool. Before this occurs, however, a heated cover-glass is applied and the section permanently mounted. This manipulation, suggested by Huber, insures the removal of all moisture and the probable permanency of the preparation, thus avoiding the unsatisfactory plan of keeping the specimens covered with only balsam and unprotected by a cover-glass.

Gold Staining.—The gold-chloride method is useful to demonstrate nerve-endings, such as the motor plates in striated muscle. Small pieces of fresh tissue, not over 5 mm. in dimension, are placed in filtered lemon juice for 20 minutes; then washed hastily in distilled water and transferred to a 1 per cent. solution of gold chloride for 25 minutes. The tissues are again

washed hastily in distilled water and then placed in a 20 per cent. solution of formic acid, in which they remain in the dark for 24 to 48 hours. Small fragments may be teased in glycerine and if successfully stained may be mounted permanently in the same; or, if desirable, the entire piece may be hardened in ascending alcohols, sectioned, and mounted in balsam. The use of steel instruments during these manipulations must be avoided, thin glass rods of suitable size being substituted. Admirable preparations, showing nerves and connective tissue cells may be made from the corneæ of small animals, the tissue being separated into thin lamellæ before mounting.

Silver Staining.—Staining with silver nitrate, as contrasted with Golgi impregnations, is employed especially to differentiate the cell-boundaries of endothelium, since by its employment the intercellular cement substance is demonstrated as dark lines. The method is of further use in bringing to view the tissue-spaces within the dense connective tissues, as the cornea, in which the spaces then appear as irregular light figures surrounded by the brown ground-substance.

When the mesothelium, covering for instance the mesentery, is to be displayed, the tissue is cut from the recently killed animal and carefully transferred by glass rods to 1 per cent. aqueous solution of silver nitrate. After immersion for 5–10 minutes, according to the thickness of the object, the tissue is rinsed in distilled water, placed in a porcelain dish containing distilled water, and stood in the direct sunlight until reduction of the silver is completed. This is indicated by a decided reddish-brown tint and usually requires 8–15 minutes. The tissue is then transferred to a small dish of distilled water to which a few granules of sodium chloride have been added, the purpose of the latter being to arrest the action of the silver. After 10 minutes, the stained tissue is placed for 6–10 hours in 70 per cent alcohol, in the dark, followed by dehydration in alcohol, clearing, and mounting in balsam. After the reduction of the silver, staining with hematoxylin adds to the interest of the preparation by bringing out the nuclei, which otherwise are only faintly seen.

When the endothelium of the blood-vessels is to be stained, the method recommended by Huber may be followed with advantage. After the escape of the blood following incision of the exposed heart of an anesthetized animal, a glass or hard rubber cannula is inserted into the thoracic aorta and the vessels injected with a 1 per cent. solution of silver nitrate. After fifteen minutes, the inferior vena cava is cut immediately below the heart and a 4 per cent. solution of formalin (10 parts commercial formalin to 90 parts distilled water) is injected into the aorta through the same cannula. The injection of the formalin washes out the superfluous silver solution, thereby avoiding disturbing precipitates, and fixes the vessels while distended. The desired tissue is then cut from the animal, care being taken to remove the structures to be examined in pieces sufficiently supported to prevent undue distortion, immersed in 4 per cent. formalin and exposed to direct sunlight. While the latter is not necessary, reduction of the silver taking place slowly in diffuse daylight, the rapid reduction effected by sunlight is favorable to sharp and well differentiated histological pictures; it should, therefore, be employed whenever possible. After dehydration, small flat pieces of the tissue are cleared in carbol-xylol, and mounted in balsam. If protected from strong daylight, such preparations may be preserved for years with little deterioration.

Injecting Blood-Vessels.—In order to demonstrate the distribution of the smaller blood-vessels and the capillaries, advantage is taken of some means to fill the blood-channels with a colored substance. The injection-mass must meet two requirements—be transparent and not diffuse through the walls of the smallest vessels. Successful, that is complete, injection of the capillaries requires considerable experience and, even at best, is attended with an element of uncertainty, since the condition of the tissues, particularly of the vessels, influences the freedom with which the injecting fluid runs.

Two injecting masses are commonly employed, **carmine-gelatin** and **Berlin blue.** When successful the former yields very beautiful preparations, but has the disadvantage of requiring to be used while hot and with heated tissue, in order to prevent untimely solidification. The beginner will find Berlin blue more convenient, since it is used cold, runs well in unwarmed tissues, and does not extravasate. The results, moreover, are equally instructive, although in the latter perhaps less striking. The injection fluid is readily prepared by dissolving 3 gm. soluble Berlin blue in 600 cc. distilled water. A smoothly working syringe of 200–300 cc. capacity, with tightly fitting stop-cock and several appropriate cannulæ is the best instrument, since the educated hand of the operator is the surest gauge of the pressure that may be applied with safety.

A small animal, such as a young rabbit or kitten, is chloroformed and then bled to death by opening the heart or some large vein, so that the vessels are emptied as far as possible. It is advisable to undertake at first the injection of a single organ, as the liver, kidney, or lung, rather than of the entire animal. The organ is not removed and is disturbed only as much as may be necessary to expose sufficiently its chief artery. Into this a cannula of appropriate size and fitted with a stop-cock is inserted through a small slit and securely tied. In order to avoid the introduction of air, the cannula should be filled with the injecting fluid, and the stop-cock turned, before being introduced into the vessel. When the cannula is in place and secured, the syringe is filled, fitted to the cannula, the stop-cock opened and the fluid gently forced into the vessels. Great care must be exercised lest sudden and excessive pressure rupture the delicate vessels and the fluid escape. If all goes well, the injected organ soon begins to assume a bluish tint, but until the tissue appears deeply and uniformly colored the capillary injection is incomplete. Before removing the cannula, the large vessels should be secured with ligatures. The organ is then removed from the animal and placed in formalin or 70 per cent. alcohol for some time before cutting into pieces. Sections of injected organs must not be too thin, but sufficiently thick to include complete capillary loops or networks. In the case of the lungs, after injecting the blood-vessels, the tissue should be moderately distended by forcing the fixing fluid through the air-tubes, which are then ligated.

Decalcification.—For adult tissues containing bone or teeth, immerse in 10 per cent. nitric or hydrochloric acid, using 70 per cent. alcohol as the diluting fluid, and change daily for about a week. After the third day, the progress of decalcification may be tested by piercing the tissue with a sharp fine needle. For embryonic tissues containing developing bone, use 2 per cent. acid made up in 70 per cent. alcohol, and change daily. Test with a needle each day, as the process will be completed in 1–3 days. For

newborn human material 5 per cent. acid is effective. Wash in running water for a day to remove the acid completely, otherwise the sections will not stain in the usual manner. Pass into graded alcohols and embed. For large blocks of adult tissue embedding in parlodion is necessary.

American stains.—Due to the active coöperation of American biologists and dye chemists and manufacturers, satisfactory American stains are available for histologic technic. In 1922 there was organized a Commission on Standardization of Biological Stains (Dr. H. J. Conn, chairman). Samples of dyes are submitted to the Commission, and if after trial these are found satisfactory they are approved by the Commission, and are sold by the manufacturers and dealers under a label bearing the certificate of the Commission. The results up to 1925 have been included in a book "Biological Stains", and current additions are given in the journal "Stain Technology", both published by the Commission (See References on Histologic Technic, page 468).

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